=> file registry

FILE 'REGISTRY' ENTERED AT 09:27:14 ON 30 MAR 2004
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Property values tagged with IC are from the ZIC/VINITI data file
provided by InfoChem.

STRUCTURE FILE UPDATES: 29 MAR 2004 HIGHEST RN 668968-88-5
DICTIONARY FILE UPDATES: 29 MAR 2004 HIGHEST RN 668968-88-5

TSCA INFORMATION NOW CURRENT THROUGH JANUARY 6, 2004

Please note that search-term pricing does apply when
conducting SmartSELECT searches.

Crossover limits have been increased. See HELP CROSSOVER for details.

Experimental and calculated property data are now available. For more
information enter HELP PROP at an arrow prompt in the file or refer
to the file summary sheet on the web at:
http://www.cas.org/ONLINE/DBSS/registryss.html

Headings for files used

=> file marpat

FILE 'MARPAT' ENTERED AT 09:27:19 ON 30 MAR 2004
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FILE CONTENT: 1988-PRESENT (VOL 140 ISS 13)(20040326/ED)

MOST RECENT CITATIONS FOR PATENTS FROM FIVE MAJOR ISSUING AGENCIES
(COVERAGE TO THESE DATES IS NOT COMPLETE):

US 6696581 24 FEB 2004
DE 10317487 19 FEB 2004
EP 1391327 25 FEB 2004
JP 2004067651 04 MAR 2004
WO 2004019432 04 MAR 2004

Structure search limits have been raised. See HELP SLIMIT for the new,
higher limits.

=> file beilstein

FILE 'BEILSTEIN' ENTERED AT 09:27:26 ON 30 MAR 2004


FILE RELOADED ON OCTOBER 20, 2002
FILE LAST UPDATED ON DECEMBER 15, 2003

FILE COVERS 1771 TO 2003.
*** FILE CONTAINS 8,861,754 SUBSTANCES ***

>>> PLEASE NOTE: Reaction data and substance data are stored in
separate documents and can not be searched together in one

query.
Reaction data for BEILSTEIN compounds may be displayed immediately with the display codes PRE (preparations) and REA (reactions). A substance answer set retrieved after the search for a chemical name, a molecular formula or a structure search for example can be restricted to compounds with available reaction information by concatenation with PRE/FA, REA/FA or more general with RX/FA. The BEILSTEIN Registry Number (BRN) is the link between a BEILSTEIN compound and belonging reactions. For more detailed reaction searches BRNs can be selected from substance answer sets and searched in the next step as reaction partner BRNs - Reactant (RX.RBRN) or Product BRN (RX.PBRN). After a search for reaction details substance documents associated with reactants or products may be retrieved by searching RX.PBRNs or RX.RBRNs as BRNs. <<<

>>> FOR SEARCHING PREPARATIONS SEE HELP PRE <<<

```
**********************************************************************
* PLEASE NOTE THAT THERE ARE NO FORMATS FREE OF COST.                *
* SET NOTICE FEATURE: THE COST ESTIMATES CALCULATED FOR SET NOTICE   *
* ARE BASED ON THE HIGHEST PRICE CATEGORY. THEREFORE; THESE          *
* ESTIMATES MAY NOT REFLECT THE ACTUAL COSTS.                        *
* FOR PRICE INFORMATION SEE HELP COST                                *
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=> file hcaplus

FILE 'HCAPLUS' ENTERED AT 09:27:32 ON 30 MAR 2004
USE IS SUBJECT TO THE TERMS OF YOUR STN CUSTOMER AGREEMENT.
PLEASE SEE "HELP USAGETERMS" FOR DETAILS.


FILE COVERS 1907 - 30 Mar 2004 VOL 140 ISS 14
FILE LAST UPDATED: 29 Mar 2004 (20040329/ED)

This file contains CAS Registry Numbers for easy and accurate substance identification.

=> FIL STNGUIDE

FILE 'STNGUIDE' ENTERED AT 09:27:38 ON 30 MAR 2004
USE IS SUBJECT TO THE TERMS OF YOUR CUSTOMER AGREEMENT


FILE CONTAINS CURRENT INFORMATION.

```
LAST RELOADED: Mar 26, 2004 (20040326/UP).

=> file belstein
'BELSTEIN' IS NOT A VALID FILE NAME
SESSION CONTINUES IN FILE 'STNGUIDE'
Enter "HELP FILE NAMES" at an arrow prompt (=>) for a list of files
that are available.  If you have requested multiple files, you can
specify a corrected file name or you can enter "IGNORE" to continue
accessing the remaining file names entered.

=> file beilstein
FILE 'BEILSTEIN' ENTERED AT 09:27:56 ON 30 MAR 2004
COPYRIGHT (c) 2004 Beilstein-Institut zur Foerderung der Chemischen Wissenschaften
licensed to Beilstein GmbH and MDL Information Systems GmbH

FILE RELOADED ON OCTOBER 20, 2002
FILE LAST UPDATED ON DECEMBER 15, 2003

FILE COVERS 1771 TO 2003.
*** FILE CONTAINS  8,861,754 SUBSTANCES ***

>>> PLEASE NOTE: Reaction data and substance data are stored in
    separate documents and can not be searched together in one
    query.
    Reaction data for BEILSTEIN compounds may be displayed
    immediately with the display codes PRE (preparations) and REA
    (reactions). A substance answer set retrieved after the search
    for a chemical name, a molecular formula or a structure search
    for example can be restricted to compounds with available
    reaction information by concatenation with PRE/FA, REA/FA or
    more general with RX/FA. The BEILSTEIN Registry Number (BRN)
    is the link between a BEILSTEIN compound and belonging reactions.
    For more detailed reaction searches BRNs can be selected from
    substance answer sets and searched in the next step as reaction
    partner BRNs - Reactant (RX.RBRN) or Product BRN (RX.PBRN).
    After a search for reaction details substance documents
    associated with reactants or products may be retrieved by
    searching RX.PBRNs or RX.RBRNs as BRNs. <<<


>>> FOR SEARCHING PREPARATIONS SEE HELP PRE  <<<

**********************************************************************
* PLEASE NOTE THAT THERE ARE NO FORMATS FREE OF COST.                 *
* SET NOTICE FEATURE: THE COST ESTIMATES CALCULATED FOR SET NOTICE    *
* ARE BASED ON THE HIGHEST PRICE CATEGORY. THEREFORE; THESE           *
* ESTIMATES MAY NOT REFLECT THE ACTUAL COSTS.                         *
* FOR PRICE INFORMATION SEE HELP COST                                 *
**********************************************************************

=>
=> FIL STNGUIDE

FILE 'STNGUIDE' ENTERED AT 09:28:16 ON 30 MAR 2004
USE IS SUBJECT TO THE TERMS OF YOUR CUSTOMER AGREEMENT
COPYRIGHT (C) 2004 AMERICAN CHEMICAL SOCIETY, JAPAN SCIENCE
AND TECHNOLOGY CORPORATION, AND FACHINFORMATIONSZENTRUM KARLSRUHE

FILE CONTAINS CURRENT INFORMATION.
LAST RELOADED: Mar 26, 2004 (20040326/UP).
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```
=> d que 15
L1          STR
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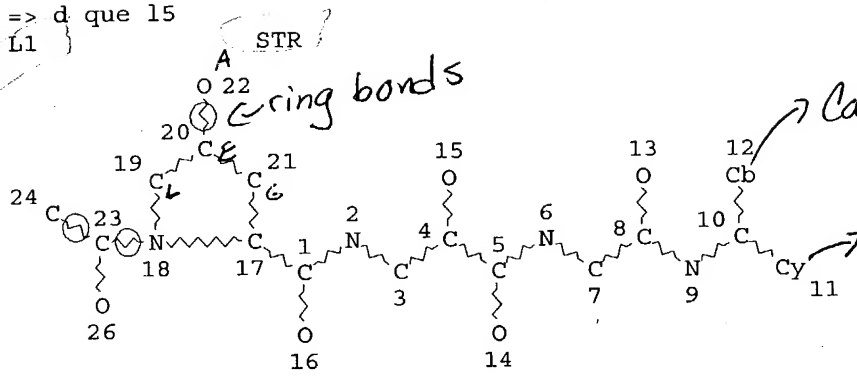


(At²) Carbocyclic Group

Cyclic Group (At¹)

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NODE ATTRIBUTES:
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CONNECT IS E1  RC AT  14
CONNECT IS E1  RC AT  15
CONNECT IS E1  RC AT  16
CONNECT IS E1  RC AT  26
DEFAULT MLEVEL IS ATOM
GGCAT   IS UNS  AT  11
GGCAT   IS UNS  AT  12
DEFAULT ECLEVEL IS LIMITED

GRAPH ATTRIBUTES:
RING(S) ARE ISOLATED OR EMBEDDED
NUMBER OF NODES IS  25

STEREO ATTRIBUTES: NONE
L2            11 SEA FILE=REGISTRY SSS FUL L1
L5             1 SEA FILE=HCAPLUS ABB=ON  PLU=ON  L2
```

exactly one non-hydrogen connection at these sites

cyclic groups at these nodes are unsaturated

```
=> d que 17
L6          STR
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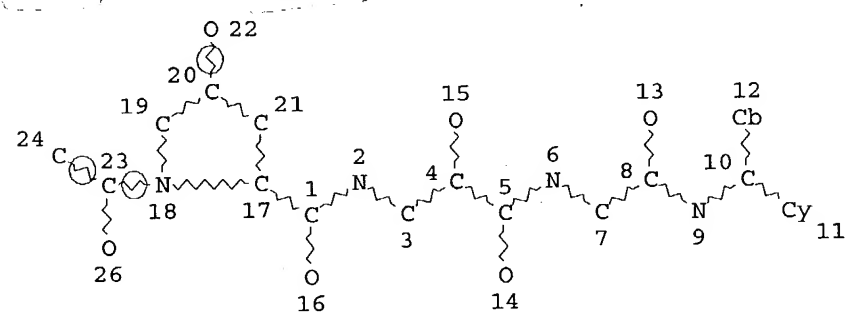


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NODE ATTRIBUTES:
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CONNECT IS E1  RC AT  26
DEFAULT MLEVEL IS ATOM
GGCAT   IS UNS  AT  11
```
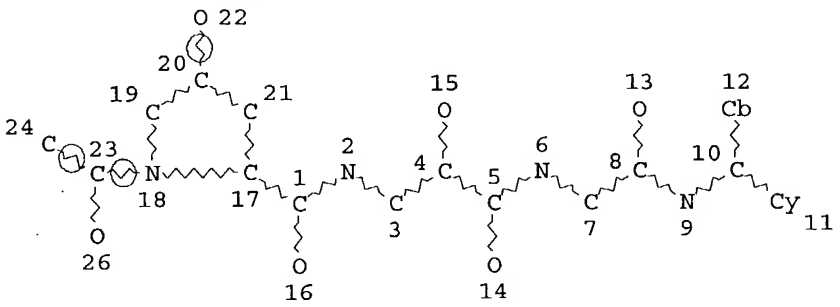

GGCAT IS UNS AT 12
DEFAULT ECLEVEL IS LIMITED

GRAPH ATTRIBUTES:
RING(S) ARE ISOLATED OR EMBEDDED
NUMBER OF NODES IS 25

STEREO ATTRIBUTES: NONE
L7 0 SEA FILE=BEILSTEIN SSS FUL L6 no hits in Beilstein

=> d que 14
L3 STR



NODE ATTRIBUTES:
CONNECT IS E1 RC AT 13
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CONNECT IS E1 RC AT 26
DEFAULT MLEVEL IS ATOM
GGCAT IS UNS AT 11
GGCAT IS UNS AT 12
DEFAULT ECLEVEL IS LIMITED

GRAPH ATTRIBUTES:
RING(S) ARE ISOLATED OR EMBEDDED
NUMBER OF NODES IS 25

STEREO ATTRIBUTES: NONE
L4 1 SEA FILE=MARPAT SSS FUL L3

=> d l5 ibib hitstr ab 1-
YOU HAVE REQUESTED DATA FROM FILE 'HCAPLUS' - CONTINUE? (Y)/N:y

YOU HAVE REQUESTED DATA FROM 1 ANSWERS - CONTINUE? Y/(N):y

L5 ANSWER 1 OF 1 HCAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2002:466030 HCAPLUS
DOCUMENT NUMBER: 137:47444
TITLE: Preparation of diaryl peptides as NS3-serine protease inhibitors of hepatitis C virus
INVENTOR(S): Zhu, Zhaoning; Sun, Zhong-Yue; Venkatraman, Srikanth; Njoroge, F. George; Arasappan, Ashok; Malcolm, Bruce A.; Girijavallabhan, Viyyoor M.; Lovey, Raymond G.; Chen, Kevin X.

PATENT ASSIGNEE(S): Schering Corporation, USA
SOURCE: PCT Int. Appl., 149 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|---|---|---|---|
| WO 2002048172 | A2 | 20020620 | WO 2001-US47383 | 20011210 |
| WO 2002048172 | A3 | 20030619 | | |
| W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, HR, HU, ID, IL, IN, IS, JP, KG, KR, KZ, LC, LK, LR, LT, LU, LV, MA, MD, MG, MK, MN, MX, MZ, NO, NZ, PH, PL, PT, RO, RU, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UZ, VN, YU, ZA, ZM, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM | | | | |
| RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG | | | | |
| AU 2002036591 | A5 | 20020624 | AU 2002-36591 | 20011210 |
| US 2002147139 | A1 | 20021010 | US 2001-13071 | 20011210 |
| EP 1343807 | A2 | 20030917 | EP 2001-986126 | 20011210 |
| R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR | | | | |

PRIORITY APPLN. INFO.: US 2000-254869P P 20001212
WO 2001-US47383 W 20011210

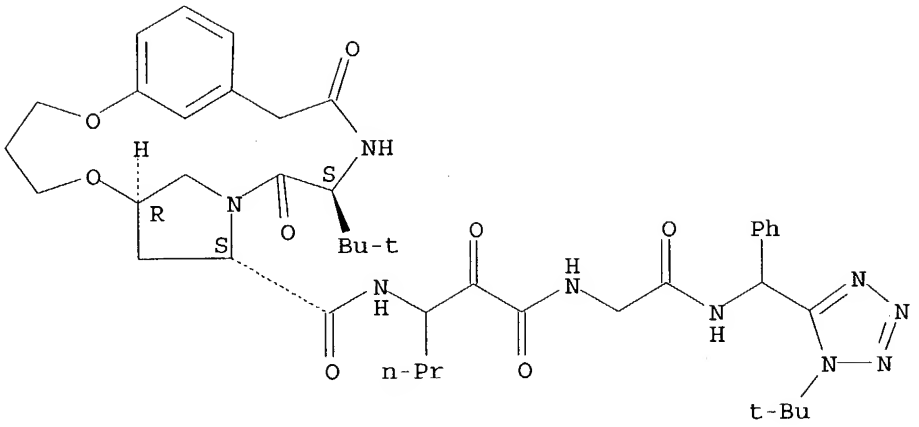
OTHER SOURCE(S): MARPAT 137:47444

IT **438041-67-9P 438041-68-0P 438041-69-1P**
**438041-70-4P 438041-71-5P 438041-72-6P**
**438041-73-7P 438041-74-8P 438041-75-9P**
RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(preparation of diaryl peptides as NS3-serine protease inhibitors of hepatitis C virus)

RN 438041-67-9 HCAPLUS

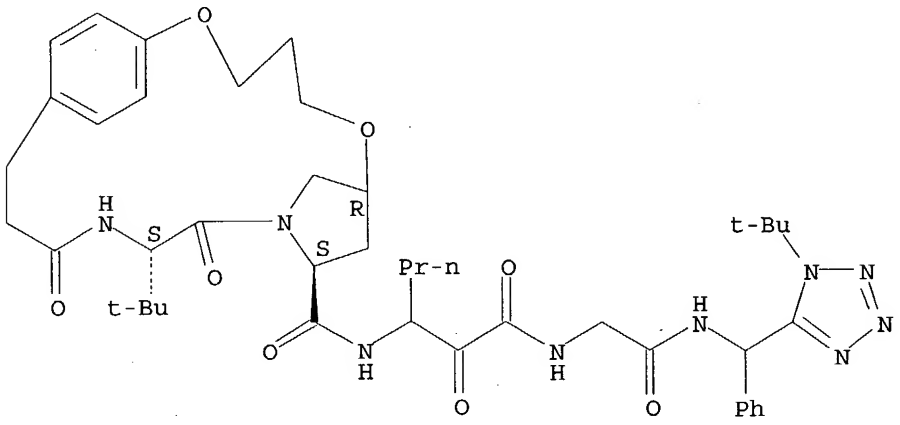
CN 2,6-Dioxa-10,13-diazatricyclo[14.3.1.17,10]heneicosa-1(20),16,18-triene-9-carboxamide, 12-(1,1-dimethylethyl)-N-[1-[[[2-[[[1-(1,1-dimethylethyl)-1H-tetrazol-5-yl]phenylmethyl]amino]-2-oxoethyl]amino]oxoacetyl]butyl]-11,14-dioxo-, (7R,9S,12S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



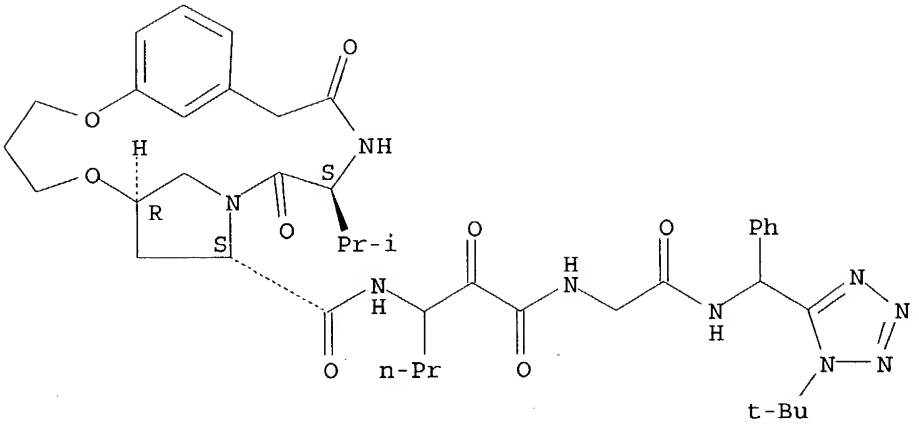
RN 438041-68-0 HCAPLUS
CN 2,6-Dioxa-10,13-diazatricyclo[15.2.2.17,10]docosa-17,19,20-triene-9-carboxamide, 12-(1,1-dimethylethyl)-N-[1-[[[2-[[[1-(1,1-dimethylethyl)-1H-tetrazol-5-yl]phenylmethyl]amino]-2-oxoethyl]amino]oxoacetyl]butyl]-11,14-dioxo-, (7R,9S,12S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



RN 438041-69-1 HCAPLUS
CN 2,6-Dioxa-10,13-diazatricyclo[14.3.1.17,10]heneicosa-1(20),16,18-triene-9-carboxamide, N-[1-[[[2-[[[1-(1,1-dimethylethyl)-1H-tetrazol-5-yl]phenylmethyl]amino]-2-oxoethyl]amino]oxoacetyl]butyl]-12-(1-methylethyl)-11,14-dioxo-, (7R,9S,12S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



RN 438041-70-4 HCAPLUS
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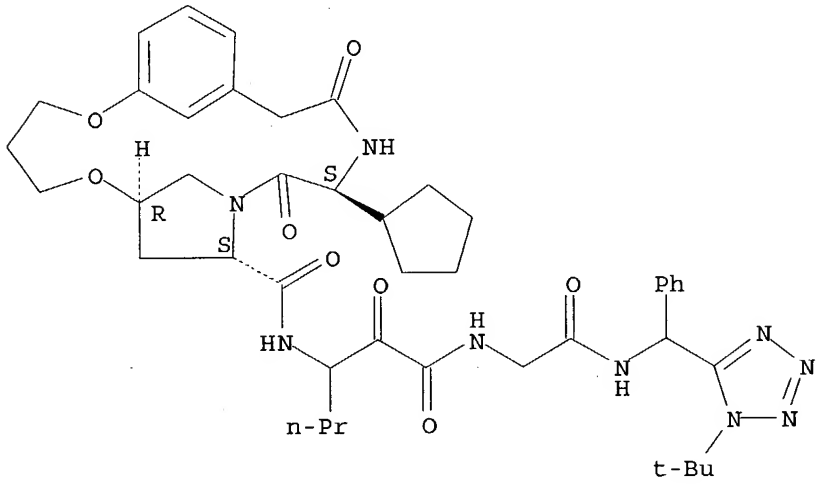
Absolute stereochemistry.



RN 438041-71-5 HCAPLUS
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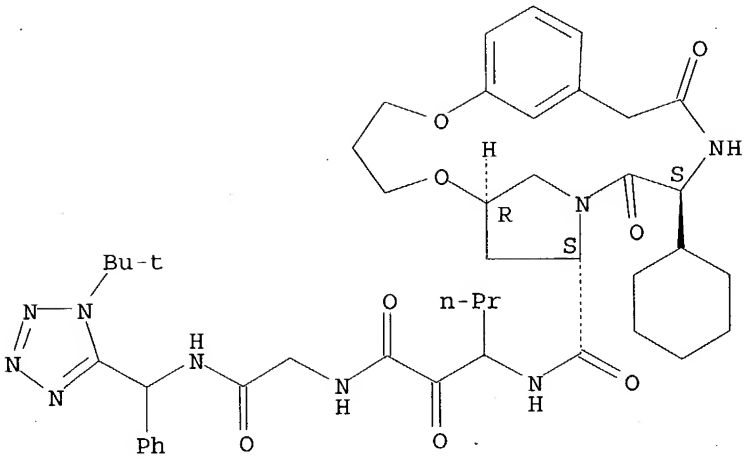
Absolute stereochemistry.



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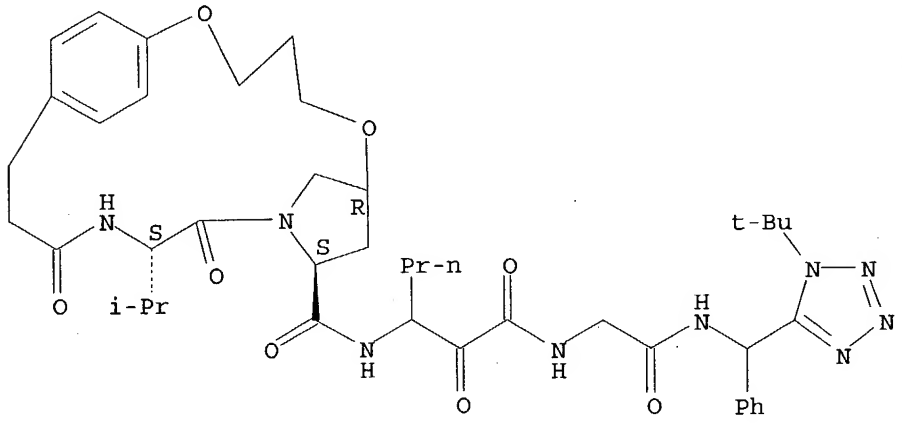
Absolute stereochemistry.



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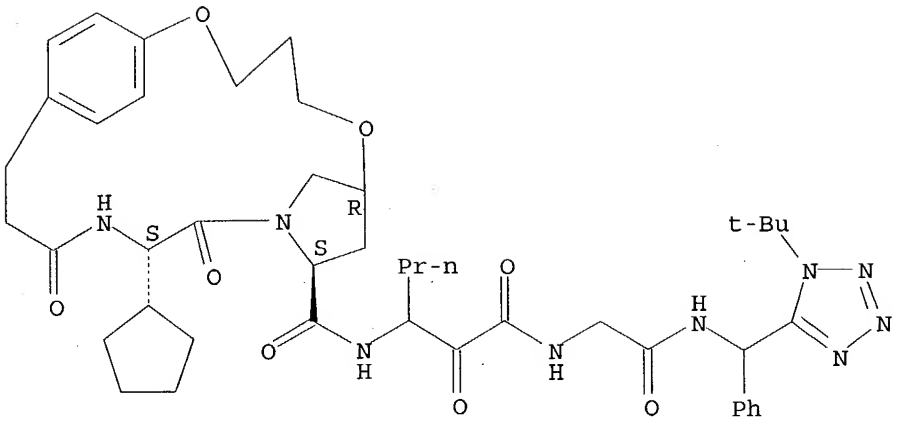
Absolute stereochemistry.



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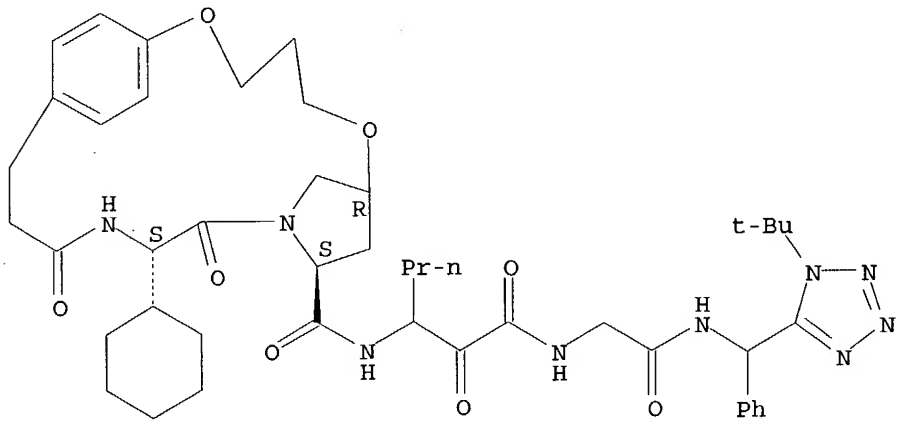
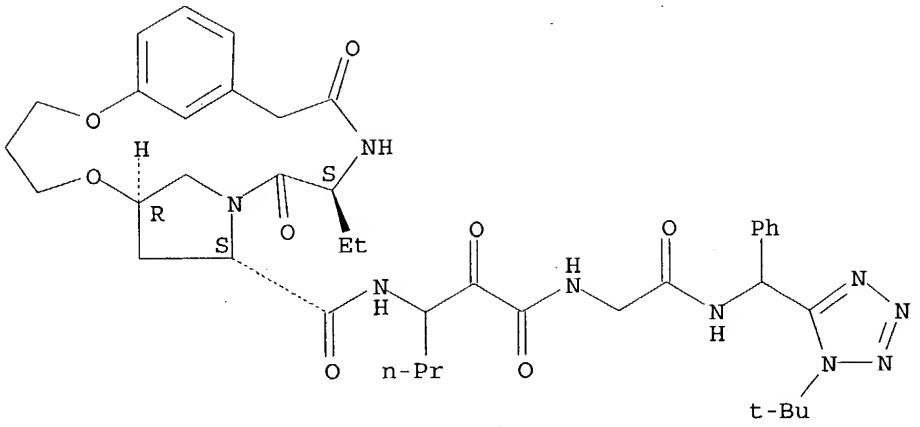
Absolute stereochemistry.



RN 438041-75-9 HCAPLUS
CN 2,6-Dioxa-10,13-diazatricyclo[14.3.1.17,10]heneicosa-1(20),16,18-triene-9-carboxamide, N-[1-[[[2-[[[1-(1,1-dimethylethyl)-1H-tetrazol-5-yl]phenylmethyl]amino]-2-oxoethyl]amino]oxoacetyl]butyl]-12-ethyl-11,14-dioxo-, (7R,9S,12S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

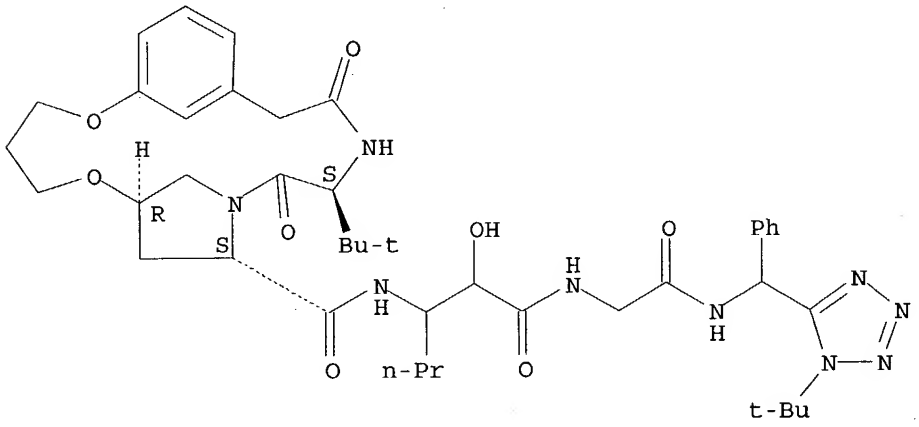


IT **438041-84-0P 438041-85-1P**
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(preparation of diaryl peptides as NS3-serine protease inhibitors of hepatitis C virus)

RN 438041-84-0 HCAPLUS

CN 2,6-Dioxa-10,13-diazatricyclo[14.3.1.17,10]heneicosa-1(20),16,18-triene-9-carboxamide, 12-(1,1-dimethylethyl)-N-[1-[2-[[2-[[[1-(1,1-dimethylethyl)-1H-tetrazol-5-yl]phenylmethyl]amino]-2-oxoethyl]amino]-1-hydroxy-2-oxoethyl]butyl]-11,14-dioxo-, (7R,9S,12S)- (9CI) (CA INDEX NAME)

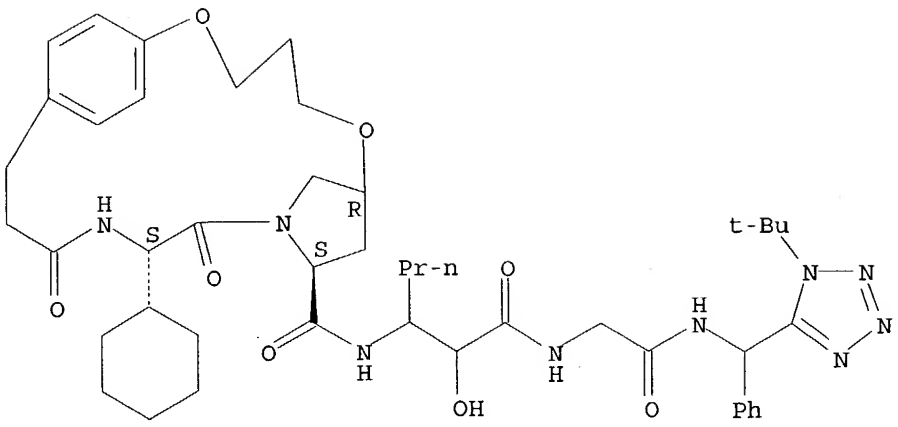
Absolute stereochemistry.



RN 438041-85-1 HCAPLUS

CN 2,6-Dioxa-10,13-diazatricyclo[15.2.2.17,10]docosa-17,19,20-triene-9-carboxamide, 12-cyclohexyl-N-[1-[2-[[2-[[[1-(1,1-dimethylethyl)-1H-tetrazol-5-yl]phenylmethyl]amino]-2-oxoethyl]amino]-1-hydroxy-2-oxoethyl]butyl]-11,14-dioxo-, (7R,9S,12S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.




AB Title compds. I [X, Y = (cyclo)alkyl, heteroalkyl, (aryl)heteroaryl, alkyl(hetero)aryl, substituted ether, sulfide, sulfone, amide, sulfonamide, urea, carbamate, hydrazide, carbonyl, etc.; W = null, CO, CS, or SO2; Q = null, CH, N, P, alkylene, O, imino, S, or SO2; A = O, CH2, alkylene, imino, S, SO2, or a bond; E = CH or substituted methylidyne, N, or a double bond toward A, L, or G; G = null or alkylene; J = null or alkylene, SO2, imino, or O; L = null or CH or substituted methylidyne, O, S, or imino; M = null or O, imino, S, SO2, or alkylene; P1a, P1b, P1', P3 = H, alkyl, alkenyl, cycloalkyl, heterocyclyl, (cycloalkyl)alkyl, or (heterocyclyl)alkyl; P1aP1bC may form a ring; Z = O or imino; Ar1, Ar2 = (un)substituted Ph, 2-, 3-, or 4-pyridyl or their N-oxides, 2- or 3-furanyl, etc.; P4 = H, alkyl, arylalkyl, or aryl; R2 = H, cyano, CF3, (cyclo)alkyl, aryl, carboxy, etc. (with provisos)] were prepared as hepatitis C virus (HCV) protease inhibitors. Thus, compound II was prepared by a multi-step procedure and showed Ki = 100-999 nM for inhibition of serine protease.

=>
=> d l4 ibib hit abs 1-
YOU HAVE REQUESTED DATA FROM FILE 'MARPAT' - CONTINUE? (Y)/N:y

YOU HAVE REQUESTED DATA FROM 1 ANSWERS - CONTINUE? Y/(N):y

L4 ANSWER 1 OF 1 MARPAT COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 137:47444 MARPAT
TITLE: Preparation of diaryl peptides as NS3-serine protease inhibitors of hepatitis C virus
INVENTOR(S): Zhu, Zhaoning; Sun, Zhong-Yue; Venkatraman, Srikanth; Njoroge, F. George; Arasappan, Ashok; Malcolm, Bruce A.; Girijavallabhan, Viyyoor M.; Lovey, Raymond G.; Chen, Kevin X.
PATENT ASSIGNEE(S): Schering Corporation, USA
SOURCE: PCT Int. Appl., 149 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|---|---|---|---|

| | | | | |
|---|---|---|---|---|
| WO 2002048172 | A2 | 20020620 | WO 2001-US47383 | 20011210 |
| WO 2002048172 | A3 | 20030619 | | |

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, HR, HU, ID, IL, IN, IS, JP, KG, KR, KZ, LC, LK, LR, LT, LU, LV, MA, MD, MG, MK, MN, MX, MZ, NO, NZ, PH, PL, PT, RO, RU, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UZ, VN, YU, ZA, ZM, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM

RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

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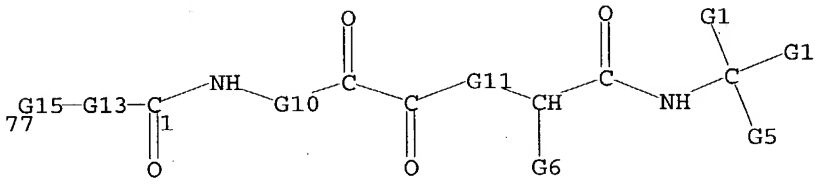
| AU 2002036591 | A5 | 20020624 | AU 2002-36591 | 20011210 |
| US 2002147139 | A1 | 20021010 | US 2001-13071 | 20011210 |
| EP 1343807 | A2 | 20030917 | EP 2001-986126 | 20011210 |

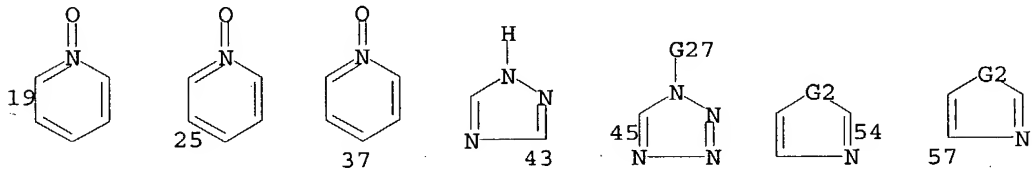
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR

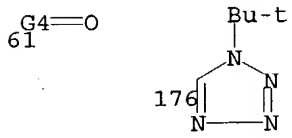
PRIORITY APPLN. INFO.: US 2000-254869P 20001212
WO 2001-US47383 20011210

**MSTR 1**

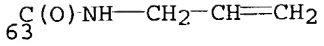



G1 = **Ph (SO (1-) G3)** / pyridyl / 19 / 25 / 37 / thienyl / furyl / pyrrolyl / imidazolyl / 43 / 45 / 54 / 57 / Hy<EC (5-6) A (1-3) Q (0-3) N (0-1) O (0-1) S (0) OTHERQ, AR (1-), BD (2-) D, RC (1), RS (1) M5 (1) X6> (SO (1-) G3) / 61 / (SC 176)

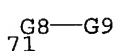


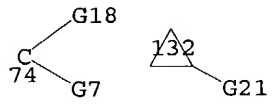

G2 = S / O
G3 = R / (SC CF3 / Me / alkyl / alkenyl)
G4 = Hy<EC (6) A (1) Q (1) N (0) OTHERQ (5) C, AN (1-) N (0-) C, AR (1-), BD (6) N, RC (1), RS (1) E6> (SO (1-) G3)
G5 = H / R / (SC alkyl / alkenyl / alkoxycarbonyl / 63)



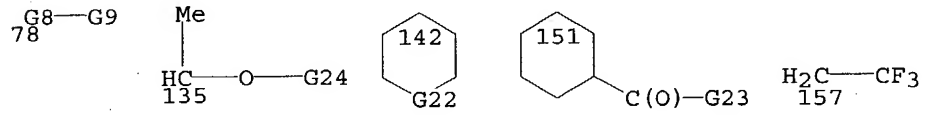
G6 = H / alkyl<(1-10)> (SO) / alkenyl<(2-10)> (SO) / cycloalkyl<(3-8)> (SO) / Hy<EC (1-6) Q (0-) N (0-) O (0-) S (0-) P (0) OTHERQ (-8) C> (SO) / 71 / aryl (SO) / heteroaryl (SO) / (SC Me)

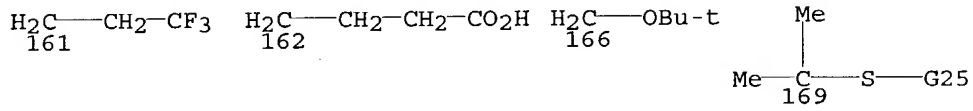


G7 = H / R
G8 = alkylene<(1-6)> (SO)
G9 = cycloalkyl<(3-8)> (SO) / Hy<EC (1-6) Q (0-) N (0-) O (0-) S (0-) P (0) OTHERQ> (SO) / aryl (SO) / heteroaryl (SO)
G10 = **74** / Cb (SO) / Hy<EC (1-6) Q (0-) N (0-) O (0-) S (0-) P (0) OTHERQ (1-) C, AN (1-) C> (SO) / (SC 132)

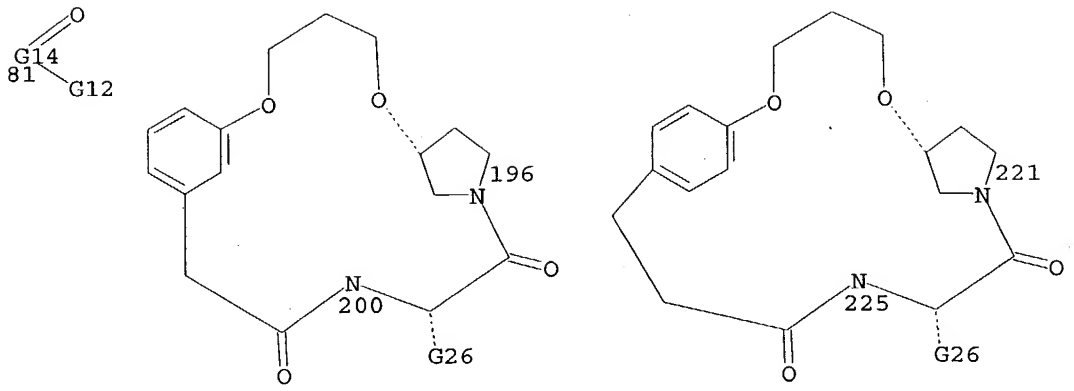


G11 = O / **NH (SO)**
G12 = H / alkyl<(1-10)> (SO) / alkenyl<(2-10)> (SO) / cycloalkyl<(3-8)> (SO) / Hy<EC (1-6) Q (0-) N (0-) O (0-) S (0-) P (0) OTHERQ (-8) C> (SO) / 78 / aryl (SO) / heteroaryl (SO) / (SC Pr-i / Me / Et / Pr-n / Bu-n / Bu-t / Bu-s / Bu-i / cyclopropyl / cyclobutyl / cyclopentyl / cyclohexyl / 135 / Ph / 142 / 151 / 157 / 161 / CH2CO2H / CH2CH2CO2H / 162 / CH(OH)Me / 166 / 169)

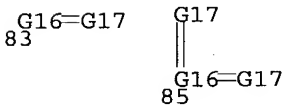




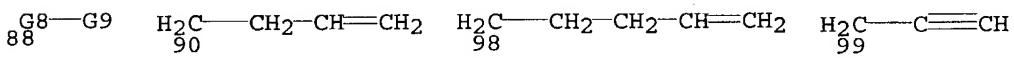
G13 = 81 / **(SC 200-77 196-1** / 225-77 221-1 )

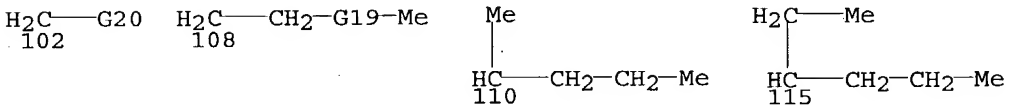


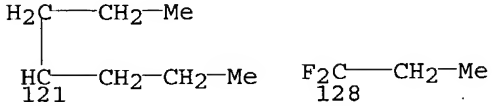
G14 = Hy<EC (1-) N (0-) O (0-) S (3-) C, AN (2-) C> (SO) / 83 / 85



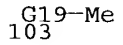
G15 = H / alkyl / aralkyl / aryl / (SC Bu-t / Bu-i / Ph)
G16 = Hy<EC (1-) N (0-) O (0-) S (3-) C, AN (2-) C> (SO)
G17 = O / S
G18 = H / alkyl<(1-10)> (SO) / alkenyl<(2-10)> (SO) / cycloalkyl<(3-8)> (SO) / Hy<EC (1-6) Q (0-) N (0-) O (0-) S (0-) P (0) OTHERQ (-8) C> (SO) / 88 / aryl (SO) / heteroaryl (SO) / (SC Me / Et / Pr-n / Bu-n / pentyl / 90 / 98 / CH2CH=CH2 / 99 / Pr-i / Bu-i / Bu-s / CH2CH2CHMe2 / 102 / 108 / 110 / 115 / 121 / CF3 / 128)







G19 = O / S / S(O) / SO2
G20 = 103 / cyclopropyl / cyclobutyl



G21 = Me / Et / CH=CH2 / cyclopropyl
G22 = O / CF2 / 146 / S(O)

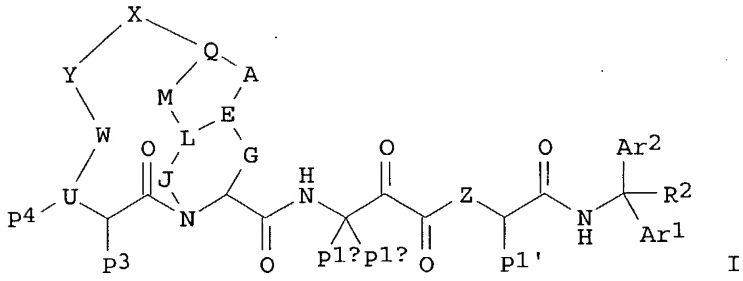
HC(146)—C(O)—G23

G23 = OH / alkoxy
G24 = CH2Ph / Bu-t
G25 = CH2Ph / Me / 173

H2C(173)—C(O)-OEt

G26 = Pr-i / Bu-t / cyclopentyl / cyclohexyl
G27 = H / R / (SC CF3 / Me / alkyl / alkenyl / Bu-t)
MPL: claim 1
NTE: and pharmaceutically acceptable salts, solvates or derivatives, or tautomers
STE: and enantiomers, stereoisomers and rotomers

GI

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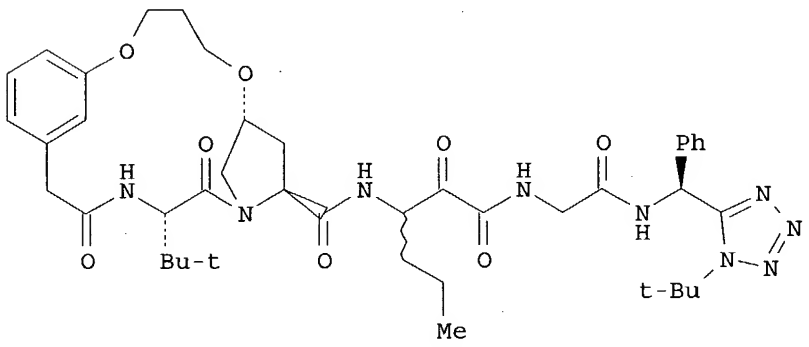


II

AB Title compds. I [X, Y = (cyclo)alkyl, heteroalkyl, (aryl)heteroaryl, alkyl(hetero)aryl, substituted ether, sulfide, sulfone, amide, sulfonamide, urea, carbamate, hydrazide, carbonyl, etc.; W = null, CO, CS, or SO2; Q = null, CH, N, P, alkylene, O, imino, S, or SO2; A = O, CH2,

alkylene, imino, S, SO2, or a bond; E = CH or substituted methylidyne, N, or a double bond toward A, L, or G; G = null or alkylene; J = null or alkylene, SO2, imino, or O; L = null or CH or substituted methylidyne, O, S, or imino; M = null or O, imino, S, SO2, or alkylene; P1a, P1b, P1', P3 = H, alkyl, alkenyl, cycloalkyl, heterocyclyl, (cycloalkyl)alkyl, or (heterocyclyl)alkyl; P1aP1bC may form a ring; Z = O or imino; Ar1, Ar2 = (un)substituted Ph, 2-, 3-, or 4-pyridyl or their N-oxides, 2- or 3-furanyl, etc.; P4 = H, alkyl, arylalkyl, or aryl; R2 = H, cyano, CF3, (cyclo)alkyl, aryl, carboxy, etc. (with provisos)] were prepared as hepatitis C virus (HCV) protease inhibitors. Thus, compound II was prepared by a multi-step procedure and showed Ki = 100-999 nM for inhibition of serine protease.

=>

=> file zcaplus

FILE 'ZCAPLUS' ENTERED AT 13:28:38 ON 30 MAR 2004
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FILE COVERS 1907 - 30 Mar 2004 VOL 140 ISS 14
FILE LAST UPDATED: 29 Mar 2004 (20040329/ED)

This file contains CAS Registry Numbers for easy and accurate substance identification.

=> file hcaplus

FILE 'HCAPLUS' ENTERED AT 13:28:43 ON 30 MAR 2004
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FILE COVERS 1907 - 30 Mar 2004 VOL 140 ISS 14
FILE LAST UPDATED: 29 Mar 2004 (20040329/ED)

This file contains CAS Registry Numbers for easy and accurate substance identification.

=> file biosis

FILE 'BIOSIS' ENTERED AT 13:28:46 ON 30 MAR 2004


FILE COVERS 1969 TO DATE.
CAS REGISTRY NUMBERS AND CHEMICAL NAMES (CNs) PRESENT FROM JANUARY 1969 TO DATE.

RECORDS LAST ADDED: 24 March 2004 (20040324/ED)

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FILE RELOADED: 19 October 2003.

=> FIL STNGUIDE

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FILE CONTAINS CURRENT INFORMATION.
LAST RELOADED: Mar 26, 2004 (20040326/UP).

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L14          13 SEA FILE=HCAPLUS ABB=ON  PLU=ON  L12 AND PROTEASE (3A)
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=> dup rem l14 l29

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PROCESSING COMPLETED FOR L29
L30           20 DUP REM L14 L29 (1 DUPLICATE REMOVED)
                ANSWERS '1-13' FROM FILE HCAPLUS
                ANSWERS '14-20' FROM FILE BIOSIS

=> d l30 ibib abs 1-13

L30 ANSWER 1 OF 20  HCAPLUS COPYRIGHT 2004 ACS on STN DUPLICATE 1
ACCESSION NUMBER:         2001:468182  HCAPLUS
DOCUMENT NUMBER:          135:73332
TITLE:                    Peptide substrates for hepatitis C virus NS3
                          protease assays
INVENTOR(S):              Zhang, Rumin; Malcolm, Bruce A.; Beyer,
                          Brian M.; Njoroge, F. George; Durkin, James
                          P.; Windsor, William T.
PATENT ASSIGNEE(S):       Schering Corp., USA
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remove Duplicates

SOURCE: U.S., 21 pp.
CODEN: USXXAM
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|---|---|---|---|
| US 6251583 | B1 | 20010626 | US 1999-288391 | 19990408 |

PRIORITY APPLN. INFO.: US 1998-83204P P 19980427

AB Novel chromogenic, fluorogenic, and fluorescence polarization substrates are provided which are useful in hepatitis C virus (HCV) NS3 **protease** and **inhibitor** assays. The peptide substrates are derived from the NS4A/4B, NS4B/5A, and NS5A/5B cleavage sites of the polyprotein. Kinetic parameters (kcat, Km, and kcat/Km) were determined for various substrates with the NS3 protease comprising a non-covalent complex of full-length 631-residue HCV Ia(H) with amino acids 1-54 of the NS4A cofactor. Preferred synthetic protocols for nitroanilide-based and nitrophenyl ester-based chromophoric substrates are also provided.

REFERENCE COUNT: 28 THERE ARE 28 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L30 ANSWER 2 OF 20 HCAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2003:591204 HCAPLUS
DOCUMENT NUMBER: 139:149928
TITLE: Preparation of peptides as NS3-serine **protease** **inhibitors** of **hepatitis** C virus
INVENTOR(S): Saksena, Anil K.; **Girijavallabhn, Viyyoor M.** ; **Lovey, Raymond G.**; Jao, Edwin; Bennett, Frank; McCormick, Jinping L.; Wang, Haiyan; Pike, Russell E.; Bogen, Stephane L.; Chan, Tin-yau; Liu, Yi-tsung; **Zhu, Zhaoning**; **Njoroge, George F.**; **Arasappan, Ashok**; Parekh, Tejal; Ganguly, Ashit K.; **Chen, Kevin X.**; **Venkatraman, Srikanth**; Vaccaro, Henry A.; Pinto, Patrick A.; Santhanam, Bama; Kemp, Scott Jeffrey; Levy, Odile Esther; Lim-Wilby, Marguerita; Tamura, Susan Y.; Wu, Wanli; Hendrata, Siska; Huang, Yuhua; Wong, Jesse K.; Nair, Latha G.
PATENT ASSIGNEE(S): Schering Corporation, USA; Corvas International, Inc.
SOURCE: PCT Int. Appl., 633 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|---|---|---|---|
| WO 2003062265 | A2 | 20030731 | WO 2003-US1430 | 20030116 |

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, HR, HU, ID, IL, IN, IS, JP, KG, KR, KZ, LC, LK, LR, LT, LU, LV, MA, MD, MG, MK, MN, MX, MZ, NO, NZ, PH, PL, PT, RO, RU, SC, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UZ, VC, VN, YU, ZA, ZM, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW,

ML, MR, NE, SN, TD, TG
PRIORITY APPLN. INFO.: US 2002-52386 A 20020118
OTHER SOURCE(S): MARPAT 139:149928
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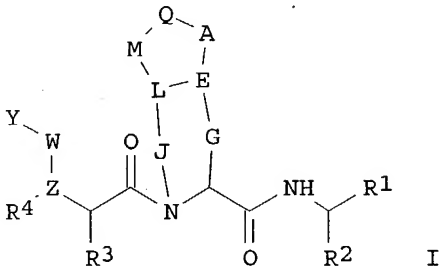

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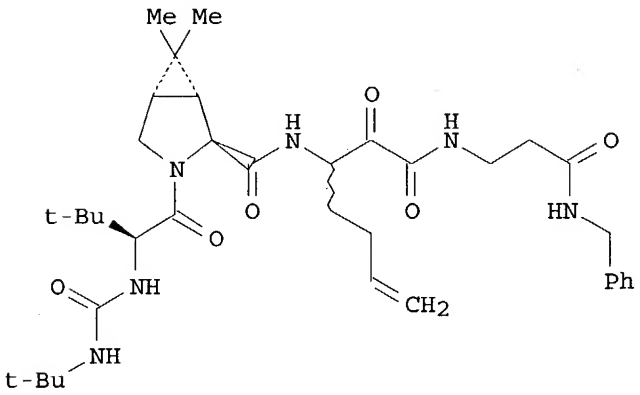

II

AB The invention discloses novel peptides I [Y is alkyl, alkylaryl, heteroalkyl, heteroaryl, aryl- or alkylheteroaryl, cycloalkyl, alkyloxy, alkylaryloxy, aryloxy, heteroaryloxy, heterocycloalkyloxy, cycloalkyloxy, alkylamino, arylamino, alkylarylamino, arylamino, heteroarylamino, cycloalkylamino, or heterocycloalkylamino; R1 is acyl; Z is selected from O, N, CH or CR; R, R2-R4 are H, alkyl, alkenyl, cycloalkyl, heterocycloalkyl, alkoxy, aryloxy, alkylthio, arylthio, amino, amido, ester, carboxylic acid, carbamate, urea, ketone, aldehyde, cyano, nitro, halo, (cycloalkyl)alkyl, or (heterocycloalkyl)alkyl; W, Q, G, J, L, M independently may be present or absent; W is CO, CS, C(:N-CN), or SO2; Q is CH, N, P, alkylidene, O, NR, S, or SO2; A is O, CH, alkylidene, NR, S, SO2, or a bond; E is CH, N, alkylidene, or a double bond; G is alkylidene; J is alkylidene, SO2, NH, NR, or O; L is CH, CR, O, S, or NR; M is O, NR, S, SO2, or alkylidene (with provisos)] which have HCV protease inhibitory activity as well as methods for preparing such compds. In another embodiment, the invention discloses pharmaceutical compns. comprising such compds. as well as methods of using them to treat disorders associated with the HCV protease. Thus, peptide II was prepared and showed Ki = 1-100 nM (category A) in the HCV continuous assay.

L30 ANSWER 3 OF 20 HCAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2003:591172 HCAPLUS
DOCUMENT NUMBER: 139:133841
TITLE: Preparation of proline compounds as NS3-serine

**protease inhibitors** for use in treatment of **hepatitis** C virus infection

INVENTOR(S): **Arasappan, Ashok**; Bennett, Frank; Bogen, Stephane L.; **Chen, Kevin X.**; Jao, Edwin; Liu, Yi-tsung; **Lovey, Raymond G.**; Madison, Vincent S.; Nair, Latha G.; **Njoroge, F. George**; Saksena, Anil K.; Sannigrahi, Mousumi; **Venkatraman, Srikanth**; **Girijavallabhan, Viyyoor M.**

PATENT ASSIGNEE(S): Schering Corporation, USA

SOURCE: PCT Int. Appl., 86 pp.
CODEN: PIXXD2

DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|---|---|---|---|
| WO 2003062228 | A1 | 20030731 | WO 2003-US1752 | 20030121 |
| W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, HR, HU, ID, IL, IN, IS, JP, KG, KR, KZ, LC, LK, LR, LT, LU, LV, MA, MD, MG, MK, MN, MX, MZ, NO, NZ, PH, PL, PT, RO, RU, SC, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UZ, VC, VN, YU, ZA, ZM, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM | | | | |
| RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG | | | | |
| US 2003207861 | A1 | 20031106 | US 2003-348094 | 20030121 |

PRIORITY APPLN. INFO.: US 2002-350931P P 20020123

OTHER SOURCE(S): MARPAT 139:133841

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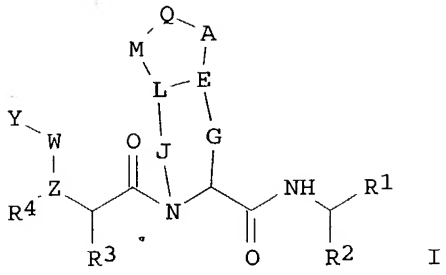

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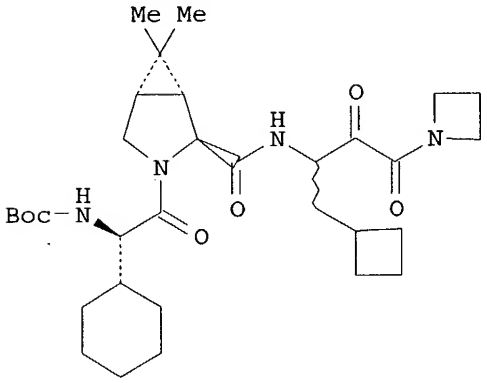

II

AB The invention discloses novel peptides I [Y is alkyl, alkylaryl, heteroalkyl, heteroaryl, aryl- or alkylheteroaryl, cycloalkyl, alkyloxy, alkylaryloxy, aryloxy, heteroaryloxy, heterocycloalkyloxy, cycloalkyloxy, alkylamino, arylamino, alkylarylamino, arylamino, heteroarylamino, cycloalkylamino, or heterocycloalkylamino; R1 is (un)substituted 1-aziridinyl, 1-azetidinyl, pyrrolidinyl, or piperidinyl; Z is selected from O, N, CH or CR; R, R2-R4 are H, alkyl, alkenyl, cycloalkyl, heterocycloalkyl, alkoxy, aryloxy, alkylthio, arylthio, amino, amido, ester, carboxylic acid, carbamate, urea, ketone, aldehyde, cyano, nitro, halo, (cycloalkyl)alkyl, or (heterocycloalkyl)alkyl; W, Q, G, J, L, M independently may be present or absent; W is CO, CS, C(:N-CN), or SO2; Q is CH, N, P, alkylidene, O, NR, S, or SO2; A is O, CH, alkylidene, NR, S, SO2, or a bond; E is CH, N, alkylidene, or a double bond; G is alkylidene; J is alkylidene, SO2, NH, NR, or O; L is CH, CR, O, S, or NR; M is O, NR, S, SO2, or alkylidene (with provisos)] which have HCV protease inhibitory activity as well as methods for preparing such compds. In another embodiment, the invention discloses pharmaceutical compns. comprising such compds. as well as methods of using them to treat disorders associated with the HCV protease. Thus, peptide II (Boc = tert-butoxycarbonyl) was prepared and showed Ki < 5 μM for inhibition of HCV serine protease.

REFERENCE COUNT: 5 THERE ARE 5 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L30 ANSWER 4 OF 20 HCAPLUS / COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2003:912843 HCAPLUS
DOCUMENT NUMBER: 139:381756
TITLE: Preparation of peptides as NS3-serine **protease inhibitors** of **hepatitis** C virus
INVENTOR(S): Saksena, Anil K.; **Girijavallabhan, Viyyoor Moopil**; **Lovey, Raymond G.**; Jao, Edwin; Bennett, Frank; Mccormick, Jinping L.; Wang, Haiyan;

Pike, Russell E.; Bogen, Stephane L.; Chan, Tin-Yau; Liu, Yi-tsung; **Zhu, Zhaoning**; **Njoroge, F. George**; **Arasappan, Ashok**; Parekh, Tejal; Ganguly, Ashit K.; **Chen, Kevin X.**; **Venkatraman, Srikanth**; Vaccaro, Henry A.; Pinto, Patrick A.; Santhanam, Bama; Kemp, Scott Jeffrey; Levy, Odile Esther; Lim-Wilby, Marguerita; Tamura, Susan Y.; Wu, Wanli; Hendrata, Siska; Huang, Yuhua

PATENT ASSIGNEE(S): USA

SOURCE: U.S. Pat. Appl. Publ., 629 pp.
CODEN: USXXCO

DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|---|---|---|---|
| US 2003216325 | A1 | 20031120 | US 2001-908955 | 20010719 |

PRIORITY APPLN. INFO.: US 2001-908955 20010719
OTHER SOURCE(S): MARPAT 139:381756

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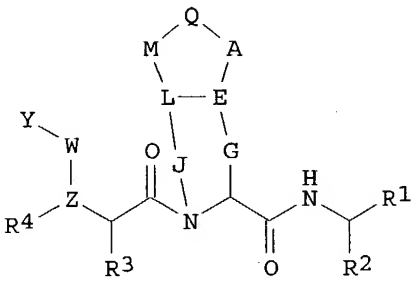

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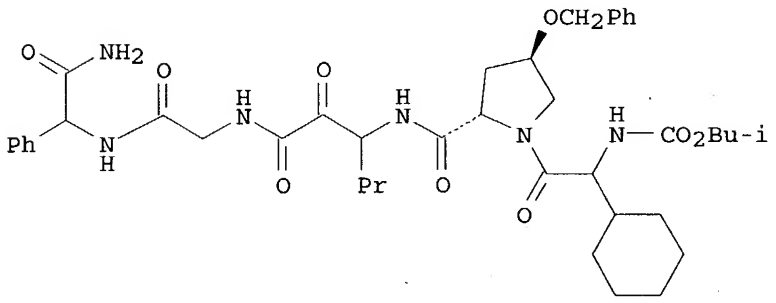


II

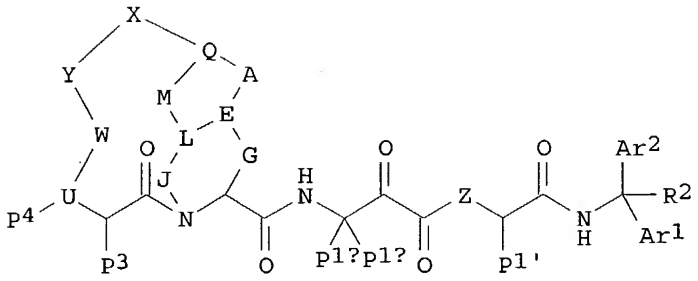
AB The invention discloses novel peptides I [Y is alkyl, alkylaryl, heteroalkyl, heteroaryl, aryl- or alkylheteroaryl, cycloalkyl, alkyloxy, alkylaryloxy, aryloxy, heteroaryloxy, heterocycloalkyloxy, cycloalkyloxy, alkylamino, arylamino, alkylarylamino, arylamino, heteroarylamino, cycloalkylamino, or heterocycloalkylamino; R1 is acyl; Z is O, N, CH or CR; R, R2-R4 are H, alkyl, alkenyl, cycloalkyl, heterocycloalkyl, alkoxy, aryloxy, alkylthio, arylthio, amino, amido, ester, carboxylic acid, carbamate, urea, ketone, aldehyde, cyano, nitro, halo, (cycloalkyl)alkyl, or (heterocycloalkyl)alkyl; W, Q, G, J, L, M independently may be present

or absent; W is CO, CS, C(:N-CN), or SO2; Q is CH, N, P, alkylidene, O, NR, S, or SO2; A is O, CH, alkylidene, NR, S, SO2, or a bond; E is CH, N, alkylidene, or a double bond; G is alkylidene; J is alkylidene, SO2, NH, NR, or O; L is CH, CR, O, S, or NR; M is O, NR, S, SO2, or alkylidene (with provisos)] which have HCV protease inhibitory activity as well as methods for preparing such compds. In another embodiment, the invention discloses pharmaceutical compns. comprising such compds. as well as methods of using them to treat disorders associated with the HCV protease. Thus, peptide II was prepared by the solid-phase method and showed Ki = 1-100 nM (category A) in the HCV continuous assay.

L30 ANSWER 5 OF 20 HCAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2002:466030 HCAPLUS
DOCUMENT NUMBER: 137:47444
TITLE: Preparation of diaryl peptides as NS3-serine **protease inhibitors** of **hepatitis** C virus
INVENTOR(S): **Zhu, Zhaoning; Sun, Zhong-Yue; Venkatraman, Srikanth; Njoroge, F. George; Arasappan, Ashok; Malcolm, Bruce A.; Girijavallabhan, Viyyoor M.; Lovey, Raymond G.; Chen, Kevin X.**
PATENT ASSIGNEE(S): Schering Corporation, USA
SOURCE: PCT Int. Appl., 149 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|---|---|---|---|
| WO 2002048172 | A2 | 20020620 | WO 2001-US47383 | 20011210 |
| WO 2002048172 | A3 | 20030619 | | |
| W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, HR, HU, ID, IL, IN, IS, JP, KG, KR, KZ, LC, LK, LR, LT, LU, LV, MA, MD, MG, MK, MN, MX, MZ, NO, NZ, PH, PL, PT, RO, RU, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UZ, VN, YU, ZA, ZM, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM | | | | |
| RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG | | | | |
| AU 2002036591 | A5 | 20020624 | AU 2002-36591 | 20011210 |
| US 2002147139 | A1 | 20021010 | US 2001-13071 | 20011210 |
| EP 1343807 | A2 | 20030917 | EP 2001-986126 | 20011210 |
| R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR | | | | |

PRIORITY APPLN. INFO.: US 2000-254869P P 20001212
WO 2001-US47383 W 20011210
OTHER SOURCE(S): MARPAT 137:47444
GI



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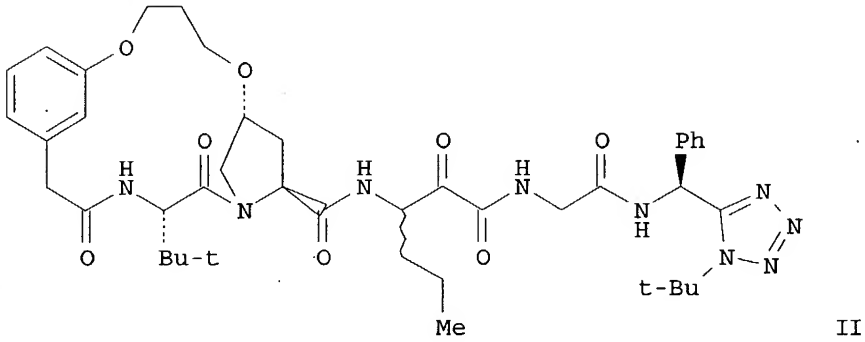

II

AB Title compds. I [X, Y = (cyclo)alkyl, heteroalkyl, (aryl)heteroaryl, alkyl(hetero)aryl, substituted ether, sulfide, sulfone, amide, sulfonamide, urea, carbamate, hydrazide, carbonyl, etc.; W = null, CO, CS, or SO2; Q = null, CH, N, P, alkylene, O, imino, S, or SO2; A = O, CH2, alkylene, imino, S, SO2, or a bond; E = CH or substituted methylidyne, N, or a double bond toward A, L, or G; G = null or alkylene; J = null or alkylene, SO2, imino, or O; L = null or CH or substituted methylidyne, O, S, or imino; M = null or O, imino, S, SO2, or alkylene; P1a, P1b, P1', P3 = H, alkyl, alkenyl, cycloalkyl, heterocyclyl, (cycloalkyl)alkyl, or (heterocyclyl)alkyl; P1aP1bC may form a ring; Z = O or imino; Ar1, Ar2 = (un)substituted Ph, 2-, 3-, or 4-pyridyl or their N-oxides, 2- or 3-furanyl, etc.; P4 = H, alkyl, arylalkyl, or aryl; R2 = H, cyano, CF3, (cyclo)alkyl, aryl, carboxy, etc. (with provisos)] were prepared as hepatitis C virus (HCV) **protease inhibitors.** Thus, compound II was prepared by a multi-step procedure and showed Ki = 100-999 nM for inhibition of serine protease.

L30 ANSWER 6 OF 20 HCAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2002:90074 HCAPLUS
DOCUMENT NUMBER: 136:151440
TITLE: Preparation of novel peptides as NS3-serine **protease inhibitors** of **hepatitis** C virus
INVENTOR(S): Saksena, Anil K.; **Girijavallabhan, Viyyoor Moopil**; **Lovey, Raymond G.**; Jao, Edwin E.; Bennett, Frank; McCormick, Jinping; Wang, Haiyan; Pike, Russell E.; Bogen, Stephane L.; Liu, Yi-Tsung; **Arasappan, Ashok**; Parekh, Tejal; Pinto, Patrick A.; **Njoroge, F. George**; Ganguly, Ashit K.; Brunck, Terence K.; Kemp, Scott Jeffrey; Levy, Odile Esther; Lim-Wilby, Marguerita

PATENT ASSIGNEE(S): Schering Corporation, USA; Corvas International, Inc.
SOURCE: PCT Int. Appl., 197 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|---|---|---|---|
| WO 2002008256 | A2 | 20020131 | WO 2001-US22826 | 20010719 |
| W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, HR, HU, ID, IL, IN, IS, JP, KG, KR, KZ, LC, LK, LR, LT, LU, LV, MA, MD, MG, MK, MN, MX, MZ, NO, NZ, PL, PT, RO, RU, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UZ, VN, YU, ZA, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM | | | | |
| RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG | | | | |
| US 2003036501 | A1 | 20030220 | US 2001-909062 | 20010719 |
| EP 1301528 | A2 | 20030416 | EP 2001-959046 | 20010719 |
| R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR | | | | |

PRIORITY APPLN. INFO.: US 2000-220109P P 20000721
WO 2001-US22826 W 20010719
OTHER SOURCE(S): MARPAT 136:151440
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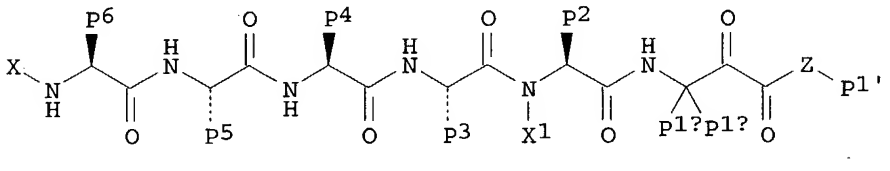


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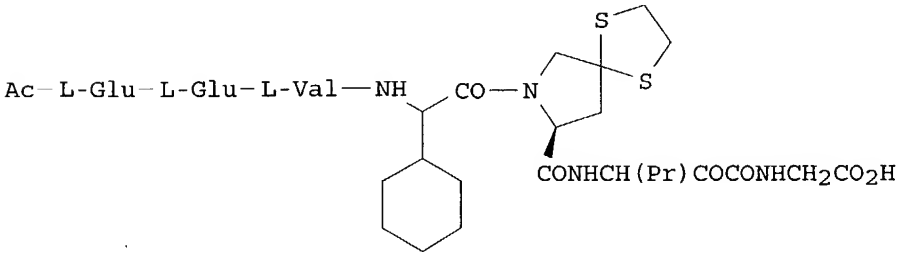


II

AB Novel peptides I [Z = O, NH or substituted imino; X = (un)substituted alkylsulfonyl, heterocyclylsulfonyl, heterocyclylalkylsulfonyl, arylsulfonyl, heteroarylsulfonyl, alkylcarbonyl, heterocyclylcarbonyl, heterocyclylalkylcarbonyl, arylcarbonyl, heteroarylcarbonyl, alkoxycarbonyl, heterocyclyloxycarbonyl, aryloxycarbonyl, heteroaryloxycarbonyl, alkyaminocarbonyl, heterocyclylaminocarbonyl,

arylaminocarbonyl, or heteroarylaminocarbonyl; X1 = H, alkyl, arylmethyl; P1a, P1b, P2-P6 = H, (un)substituted alkyl, alkenyl, cycloalkyl, heterocyclyl, cycloalkylalkyl, heterocyclylalkyl, aryl, heteroaryl, arylalkyl, or heteroarylalkyl; P1a and P1b may optionally be joined to each other to form a spirocyclic or spiroheterocyclic ring containing 0-6 oxygen, nitrogen, sulfur, or phosphorus atoms; P1' = H, (un)substituted alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkylalkyl, heterocyclyl, heterocyclylalkyl, aryl, arylalkyl, heteroaryl, or heteroarylalkyl] having HCV protease inhibitory activity are disclosed. Thus, peptide II was prepared via peptide coupling in solution and showed Ki = 1-100 nM for inhibition of HCV protease.

L30 ANSWER 7 OF 20 HCAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2002:90062 HCAPLUS
DOCUMENT NUMBER: 136:167698
TITLE: Preparation of peptides as NS3-serine **protease inhibitors** of **hepatitis** C virus
INVENTOR(S): Saksena, Anil K.; **Girijavallabhan, Viyyoor Moopil**; **Lovey, Raymond G.**; Jao, Edwin E.; Bennett, Frank; McCormick, Jinping L.; Wang, Haiyan; Pike, Russell E.; Bogen, Stephane L.; Chan, Tin-Yau; Liu, Yi-Tsung; **Zhu, Zhaoning**; **Njoroge, F. George**; **Arasappan, Ashok** ; Parekh, Tejal N.; Ganguly, Ashit K.; **Chen, Kevin X.**; **Venkatraman, Srikanth**; Vaccaro, Henry A.; Pinto, Patrick A.; Santhanam, Bama; Wu, Wanli; Hendrata, Siska; Huang, Yuhua; Kemp, Scott Jeffrey; Levy, Odile Esther; Lim-Wilby, Marguerita; Tamura, Susan Y.
PATENT ASSIGNEE(S): Schering Corporation, USA; Corvas International, Inc.
SOURCE: PCT Int. Appl., 536 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|---|---|---|---|
| WO 2002008244 | A2 | 20020131 | WO 2001-US22678 | 20010719 |
| WO 2002008244 | A3 | 20030619 | | |
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| RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG | | | | |
| AU 2001076988 | A5 | 20020205 | AU 2001-76988 | 20010719 |
| BR 2001012540 | A | 20030624 | BR 2001-12540 | 20010719 |
| EP 1385870 | A2 | 20040204 | EP 2001-954764 | 20010719 |
| R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR | | | | |
| JP 2004504404 | T2 | 20040212 | JP 2002-514149 | 20010719 |
| NO 2003000272 | A | 20030321 | NO 2003-272 | 20030120 |

PRIORITY APPLN. INFO.: US 2000-220108P P 20000721
WO 2001-US22678 W 20010719
OTHER SOURCE(S): MARPAT 136:167698

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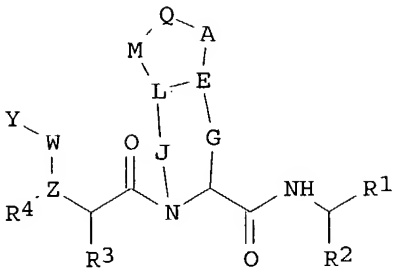

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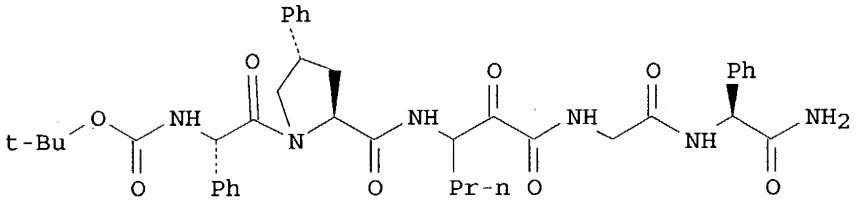


II

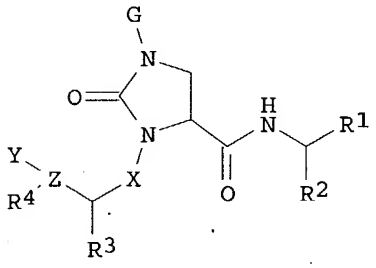
AB Peptides I were prepared wherein Y is alkyl, alkyl-aryl, heteroaryl, heteroalkyl, heteroaryl, aryl-heteroaryl, alkylheteroaryl, cycloalkyl, alkyloxy, alkylaryloxy, aryloxy, heteroaryloxy, heterocycloalkyloxy, cycloalkyloxy,, alkylamino, arylamino, alkylarylamino, arylamino, heteroarylamino, cycloalkylamino and heterocycloalkylamino; R1 is acyl, borate; Z is selected from O, N, CH or CR; W, Q, G, J, L, M independently maybe present or absent; W is C=O, C=S, C(=N-CN), or SO; Q is CH, N, P, alkylidene, O, amine,S, or SO; A is O, CH, alkylidene, amine, S, SO or bond; E is CH, N, alkylidene, or double bond; G is alkylidene; J is alkylidene, SO, NH, NR, O; L is CH, alkylidene, O, S or NR; M is O, NR,S, SO, alkylidene; p is 0 to 6; and R-R4 are independently selected from the group consisting of H; alkyl; alkenyl; cycloalkyl; heterocycloalkyl, alkoxy, aryloxy, alkylthio, arylthio, amino, amido, ester, carboxylic acid, carbamate, urea, ketone, aldehyde, cyano, nitro, halogen; (cycloalkyl)alkyl and (heterocycloalkyl)alkyl, which have HCV protease inhibitory activity as well as methods for preparing such compds. In another embodiment, the invention discloses pharmaceutical compns. comprising such compds. as well as methods of using them to treat disorders associated with the HCV protease. Thus peptide II was prepared and tested as antiviral agent and NS3-serine **protease inhibitors** of hepatitis C virus with Ki ranges in category A = 1-100 nM; category B = 101-1,000 nM; category C > 1000 nM. Also disclosed is the use of I for the manufacture of a medicament for treating HCV, AIDS, and related disorders.

L30 ANSWER 8 OF 20 HCAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2002:90018 HCAPLUS
DOCUMENT NUMBER: 136:135031
TITLE: Preparation of novel imidazolidinones as NS3-serine **protease inhibitors** of **hepatitis** C virus
INVENTOR(S): **Arasappan, Ashok**; Parekh, Tejal; **Njoroge, F. George**; **Girijavallabhan, Viyyoor Moopil**; Ganguily, Ashit K.
PATENT ASSIGNEE(S): Schering Corporation, USA

SOURCE: PCT Int. Appl., 88 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|---|---|---|---|
| WO 2002008198 | A2 | 20020131 | WO 2001-US22828 | 20010719 |
| WO 2002008198 | A3 | 20020718 | | |
| W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, HR, HU, ID, IL, IN, IS, JP, KG, KR, KZ, LC, LK, LR, LT, LU, LV, MA, MD, MG, MK, MN, MX, MZ, NO, NZ, PL, PT, RO, RU, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UZ, VN, YU, ZA, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM | | | | |
| RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG | | | | |
| US 2002102235 | A1 | 20020801 | US 2001-909077 | 20010719 |
| EP 1301486 | A2 | 20030416 | EP 2001-961676 | 20010719 |
| R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR | | | | |

PRIORITY APPLN. INFO.: US 2000-220110P P 20000721
WO 2001-US22828 W 20010719
OTHER SOURCE(S): MARPAT 136:135031
GI



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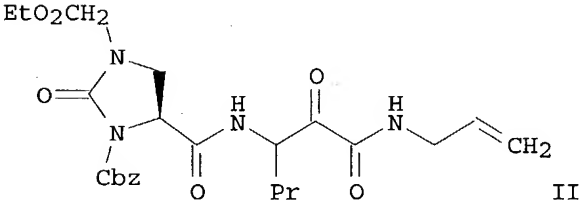


II

AB Novel imidazolidinones I [R1 = COR5 (R5 = H, OH, alkoxy, amino, CF3, etc.) or B(OR)3 (R = H, alkyl, alkyl, alkenyl, cycloalkyl, heterocycloalkyl, alkoxy, aryloxy, alkylthio, arylthio, amino, amido, ester, carboxylic acid, etc.); Z = O, N or CH; X = CO, CS or alkylene; G = H, (un)substituted alkyl, aryl, heteroalkyl, heteroaryl, alkylaryl or alkylheteroaryl; R2, R3 = any group defined for R; R4 = null, H, alkyl, aryl; Y = H, (un)substituted alkyl, aryl, heteroalkyl, heteroaryl,

cycloalkyl, arylalkyl, heteroarylalkyl, etc.], including enantiomers, stereoisomers, rotamers and tautomers, having HCV protease inhibitory activity are disclosed. Thus, compound II (Cbz = benzyloxycarbonyl) was prepared via peptide coupling reaction of H2NCHPrCH(OH)CONHCH2CH:CH2.HCl (preparation given), followed by Dess-Martin oxidation of the hydroxy group.

II

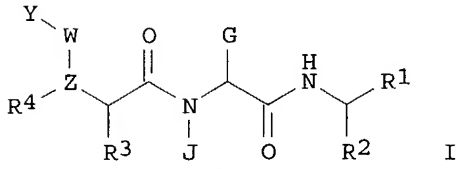
showed Ki > 50,001 nM for inhibition of HCV protease.

L30 ANSWER 9 OF 20 HCAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2002:90007 HCAPLUS
DOCUMENT NUMBER: 136:151439
TITLE: Preparation of novel peptides as NS3-serine **protease inhibitors** of **hepatitis** C virus
INVENTOR(S): Saksena, Anil K.; **Girijavallabhan, Viyyoor Moopil**; Bogen, Stephane L.; **Lovey, Raymond G.**; Jao, Edwin E.; Bennett, Frank; McCormick, Jinping L.; Wang, Haiyan; Pike, Russell E.; Liu, Yi-Tsung; Chan, Tin-Yau; **Zhu, Zhaoning**; **Arasappan, Ashok**; **Chen, Kevin X.**; **Venkatraman, Srikanth**; Parekh, Tejal N.; Pinto, Patrick A.; Santhanam, Bama; **Njoroge, F. George**; Ganguly, Ashit K.; Vaccaro, Henry A.; Kemp, Scott Jeffrey; Levy, Odile Esther; Lim-Wilby, Marguerita; Tamura, Susan Y.
PATENT ASSIGNEE(S): Schering Corporation, USA; Corvas International, Inc.
SOURCE: PCT Int. Appl., 188 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|---|---|---|---|
| WO 2002008187 | A1 | 20020131 | WO 2001-US22813 | 20010719 |
| WO 2002008187 | C2 | 20030103 | | |
| W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, HR, HU, ID, IL, IN, IS, JP, KG, KR, KZ, LC, LK, LR, LT, LU, LV, MA, MD, MG, MK, MN, MX, MZ, NO, NZ, PL, PT, RO, RU, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UZ, VN, YU, ZA, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM | | | | |
| RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG | | | | |
| US 2002160962 | A1 | 20021031 | US 2001-909012 | 20010719 |
| EP 1303487 | A1 | 20030423 | EP 2001-959041 | 20010719 |
| R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR | | | | |
| BR 2001012666 | A | 20030610 | BR 2001-12666 | 20010719 |
| NO 2003000271 | A | 20030318 | NO 2003-271 | 20030120 |

PRIORITY APPLN. INFO.: US 2000-220107P P 20000721
WO 2001-US22813 W 20010719

OTHER SOURCE(S): MARPAT 136:151439
GI



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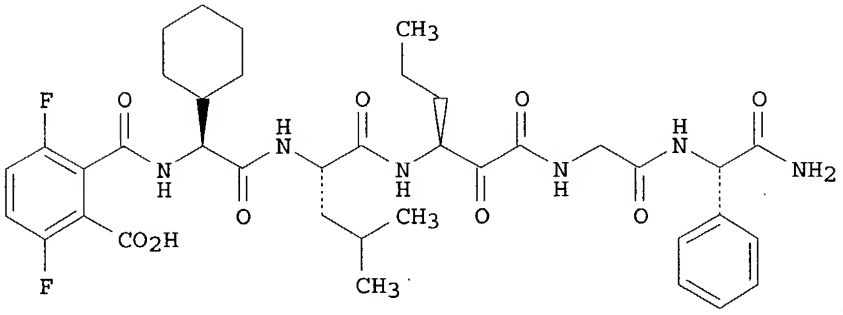

II

AB Novel peptides I [G, J, Y = independently H, alkyl, alkyl-aryl, heteroalkyl, heteroaryl, aryl-heteroaryl, alkyl-heteroaryl, cycloalkyl, alkoxy, alkyl-aryloxy, aryloxy, heteroaryloxy, heterocycloalkyloxy, cycloalkyloxy, alkylamino, arylamino, alkyl-arylamino, arylamino, heteroarylamino, cycloalkylamino, and heterocycloalkylamino; Z = O, N, CH; W = null, CO, CS, SO2; R1 = COR5, B(OR)2; R5 = H, OH, OR8, NR9R10, CF3, C2F5, C3F7, CF2R6, R6, COR7; R7 = H, OH, OR8, CHR9R10, NR9R10; R6, R8-10 = independently H, alkyl, aryl, heteroalkyl, cycloalkyl, arylalkyl, peptide derivative, etc.; R, R2-4 = independently H, alkyl, alkenyl, cycloalkyl, heterocycloalkyl, alkoxy, aryloxy, alkylthio, arylthio, amino, amido, ester, carboxylic acid, carbamate, etc.] and their pharmaceutically salts which have hepatitis C virus (HCV) protease inhibitory activity were prepared via solution or solid-phase peptide coupling methods. Thus, peptide II was prepared using solid-phase methods and showed a Ki value in the range of 0-100 nM for HCV protease inhibitory activity. This invention also discloses pharmaceutical compns. comprising such compds. as well as methods of using them to treat disorders associated with the HCV protease.

REFERENCE COUNT: 3 THERE ARE 3 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L30 ANSWER 10 OF 20 HCAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2001:798207 HCAPLUS
DOCUMENT NUMBER: 135:344735
TITLE: Preparation of macrocyclic NS3-serine **protease inhibitors** of **hepatitis** C virus comprising alkyl and aryl alanine p2 moieties
INVENTOR(S): **Venkatraman, Srikanth; Chen, Kevin X.; Arasappan, Ashok; Njoroge, F. George; Girijavallabhan, Viyyoor M.**; Chan, Tin-Yau; McKittrick, Brian A.; Prongay, Andrew J.; Madison, Vincent S.
PATENT ASSIGNEE(S): Schering Corporation, USA
SOURCE: PCT Int. Appl., 218 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|---|---|---|---|
| WO 2001081325 | A2 | 20011101 | WO 2001-US12530 | 20010417 |
| WO 2001081325 | A3 | 20020801 | | |
| W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, HR, HU, ID, IL, IN, IS, JP, KG, KR, KZ, LC, LK, LR, LT, LU, LV, MA, MD, MG, MK, MN, MX, MZ, NO, NZ, PL, PT, RO, RU, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UZ, VN, YU, ZA, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM | | | | |
| RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG | | | | |
| US 2002016294 | A1 | 20020207 | US 2001-836636 | 20010417 |
| BR 2001010104 | A | 20030107 | BR 2001-10104 | 20010417 |
| EP 1274724 | A2 | 20030115 | EP 2001-927142 | 20010417 |
| R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR | | | | |
| JP 2003531199 | T2 | 20031021 | JP 2001-578418 | 20010417 |
| NO 2002005030 | A | 20021218 | NO 2002-5030 | 20021018 |

PRIORITY APPLN. INFO.: US 2000-198204P P 20000419
WO 2001-US12530 W 20010417

OTHER SOURCE(S): MARPAT 135:344735

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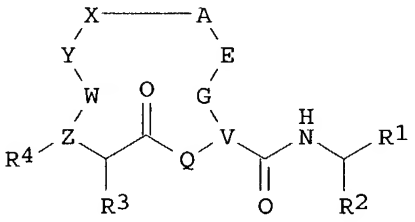


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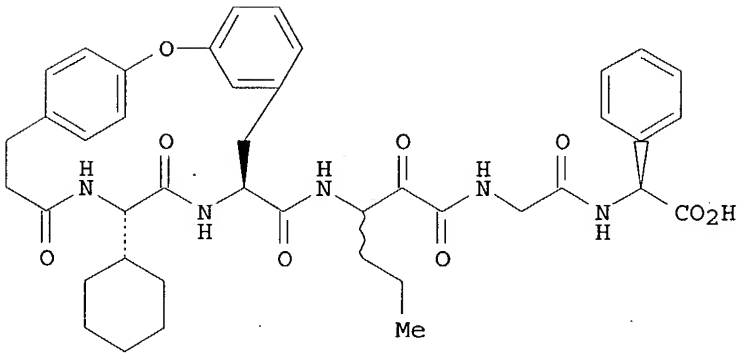


II

AB Macrocyclic compds. I [E, X, Y may be independently present or absent, and

if present may be (un)substituted (cyclo)alkyl, aryl, heteroalkyl, heteroaryl, ether, amino, sulfide, sulfone, amide, sulfonamide, urea, carbamate, hydrazide, carbonyl, etc.; R1 = acyl or boryl groups; Z = O, N, or CH; W = null, CO, CS, SO2, C:NR (R = H, alkyl, cycloalkyl, aryl, etc.); Q = (NR)p (p = 0-6), O, S, CH2, CHR, CRR' (R' = any group given for R) or a double bond toward V; A = O, CH2, (CHR)p, (CHRCHR')p, (CRR')p, NR, S, SO2, CO or a bond; G = (CH2)p, (CHR)p, (CRR')p, NR, O, S, SO2, SO2NH, CO or a bond towards E or V; R2, R3, R4 = H, (un)substituted (hetero)alkyl, -aryl or -cycloalkyl, alkoxy, aryloxy, alkylthio, arylthio, amino, amido, ester, carboxylic acid, carbamate, urea, ketone, aldehyde, cyano, nitro, etc.], including enantiomers and pharmaceutically acceptable salts, were prepared as hepatitis C virus (HCV) **protease inhibitors.** Thus, peptide II was prepared by a multistep procedure involving cyclization of intermediate cyclopentadiene-η6-ruthenium-4-chlorophenylpropionic acid-cyclohexylglycine-m-tyrosine-OMe. II showed Ki = 0.001-1.0μM in the HCV protease assay. The invention also discloses pharmaceutical compns. comprising I as well as methods of using them to treat disorders associated with the HCV protease.

L30 ANSWER 11 OF 20 HCAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2001:763001 HCAPLUS
DOCUMENT NUMBER: 135:318715
TITLE: Preparation of macrocyclic NS3-serine **protease inhibitors** of **hepatitis** C virus comprising n-cyclic p2 moieties
INVENTOR(S): **Chen, Kevin X.**; **Arasappan, Ashok**; **Venkatraman, Srikanth**; Parekh, Tejal N.; Gu, Haining; **Njoroge, F. George**; **Girijavallabhan, Viyyoor M.**; Ganguly, Ashit; Saksena, Anil; Jao, Edwin; Yao, Nanhua H.; Prongay, Andrew J.; Madison, Vincent S.; Vibulbhan, Bancha
PATENT ASSIGNEE(S): Schering Corporation, USA
SOURCE: PCT Int. Appl., 402 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|---|---|---|---|
| WO 2001077113 | A2 | 20011018 | WO 2001-US10869 | 20010403 |
| WO 2001077113 | A3 | 20020620 | | |
| W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, HR, HU, ID, IL, IN, IS, JP, KG, KR, KZ, LC, LK, LR, LT, LU, LV, MA, MD, MG, MK, MN, MX, MZ, NO, NZ, PL, PT, RO, RU, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UZ, VN, YU, ZA, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM | | | | |
| RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG | | | | |
| US 2002107181 | A1 | 20020808 | US 2001-825399 | 20010403 |
| EP 1268525 | A2 | 20030102 | EP 2001-926601 | 20010403 |
| R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR | | | | |
| BR 2001009861 | A | 20030610 | BR 2001-9861 | 20010403 |
| JP 2003530401 | T2 | 20031014 | JP 2001-575586 | 20010403 |
| NO 2002004797 | A | 20021204 | NO 2002-4797 | 20021004 |

PRIORITY APPLN. INFO.: US 2000-194607P P 20000405

WO 2001-US10869 W 20010403

OTHER SOURCE(S): MARPAT 135:318715
GI

* STRUCTURE DIAGRAM TOO LARGE FOR DISPLAY - AVAILABLE VIA OFFLINE PRINT *

AB Title compds. I [wherein X and Y = independently (cyclo)alkyl, heteroalkyl, (aryl)heteroaryl, alkyl(hetero)aryl, substituted ether, sulfide, sulfone, amide, sulfonamide, urea, carbamate, hydrazide, carbonyl, etc.; R1 = CHO, acyl, or (un)substituted carboxy, carbamoyl, boryl, etc.; Z = O, N, or CH, W = null or CO, CS, or SO2; Q = null or CH, N, P, (CH2)p, (CHR)p, (CRR')p, O, NR, S, or SO2; A = O, CH2, (CHR)p, (CHRCHR')p, (CRR')p, NR, S, SO2, or a bond; E = CH, N, CR, or a double bond toward A, L, or G; G = null or (CH2)p, (CHR)p, or (CRR')p; J = null or CH, CR, O, S, or NR; M = null or O, NR, S, SO2, "(CH2)p, (CHR)p, (CHRCHR')p, or (CRR')p; p = 0-6; R, R', R2, R3, and R4 = independently H, (cyclo)alkyl, alkenyl, heterocycloalkyl, alkoxy, aryloxy, alkylthio, arylthio, amino, amido, ester, carboxylic acid, carbamate, urea, ketone, CHO, CN, NO2, O, N, S, P, etc.] were prepared as hepatitis C virus (HCV) **protease inhibitors.** For example, II (multi-step preparation given) was cyclized, deesterified, and coupled with III•HCl (preparation given) to give the macrocyclic hydroxyamide intermediate. Oxidation using Des-Martin reagent followed by flash chromatog. afforded two diastereomers IV in 82% combined yield. The (S)-isomer inhibited NS3-serine protease HeLa/Huh7 co-transfected cells with a Ki of 2 μM. The invention also discloses pharmaceutical compns. comprising I as well as methods of using them to treat disorders associated with the HCV protease.

L30 ANSWER 12 OF 20 HCAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 1999:375680 HCAPLUS
DOCUMENT NUMBER: 131:29294
TITLE: Recombinant **hepatitis** C virus NS3 protein-NS4A cofactor fusions and their use for screening for NS3 **protease** and helicase **inhibitors**
INVENTOR(S): **Malcolm, Bruce A.**; Taremi, S. Shane; Weber, Patricia C.; Yao, Nanhua
PATENT ASSIGNEE(S): Schering Corporation, USA
SOURCE: PCT Int. Appl., 211 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|---|---|---|---|
| WO 9928482 | A2 | 19990610 | WO 1998-US24528 | 19981124 |
| WO 9928482 | A3 | 19990722 | | |
| W: AL, AM, AU, AZ, BA, BB, BG, BR, BY, CA, CN, CZ, EE, GD, GE, HR, HU, ID, IL, IS, JP, KG, KR, KZ, LC, LK, LR, LT, LV, MD, MG, MK, MN, MX, NO, NZ, PL, RO, RU, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UZ, VN, YU, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM | | | | |
| RW: GH, GM, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG | | | | |
| AU 9914160 | A1 | 19990616 | AU 1999-14160 | 19981124 |

| | | | | | |
|---|---|---|---|---|---|
| US 6211338 | B1 | 20010403 | US 1998-198723 | | 19981124 |
| US 6653127 | B1 | 20031125 | US 2000-684881 | | 20001006 |
| PRIORITY APPLN. INFO.: | | | US 1997-67315P | P | 19971128 |
| | | | US 1998-94331P | P | 19980728 |
| | | | US 1998-198723 | A3 | 19981124 |
| | | | WO 1998-US24528 | W | 19981124 |

AB Covalent HCV NS4A-NS3 complexes comprising the central hydrophobic domain of native HCV NS4A peptide, a linker, and the HCV NS3 serine protease domain, wherein the hydrophobic domain of native HCV NS4A peptide is tethered by the linker to the amino terminus of the HCV NS3 protease domain are disclosed. Also disclosed are nucleic acids encoding the fusion proteins, vectors containing said nucleic acids, and cells expressing the fusion proteins. These fusion proteins may be used for screening for inhibitors of the proteinase and helicase activities of the NS3 protein. Certain of the fusion proteins of the invention had activity equivalent to that of the native NS3-NS4A complex.

L30 ANSWER 13 OF 20 HCAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 1998:471989 HCAPLUS
DOCUMENT NUMBER: 129:199688
TITLE: Rapid mass spectrometric determination of preferred irreversible proteinase inhibitors in combinatorial libraries
AUTHOR(S): Mckendrick, John E.; Frormann, Sven; Luo, Colin; Semchuck, Paul; Vederas, John C.; **Malcolm, Bruce A.**
CORPORATE SOURCE: The Department of Chemistry, University of Alberta, Edmonton, AB, T6G 2G2, Can.
SOURCE: International Journal of Mass Spectrometry (1998), 176(1/2), 113-124
CODEN: IMSPF8; ISSN: 1387-3806
PUBLISHER: Elsevier Science B.V.
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Optimal N-iodoacetyldipeptide inactivators of hepatitis A virus 3C proteinase were identified directly from equimolar mixts. of these compds. using electrospray ionization mass spectrometry (ESI-MS). Limiting amts. of proteinase were allowed to react with the library of inhibitors and were subsequently analyzed by ESI-MS to determine the mass of the adducts formed. N-iodoacetyl-Ser-Phe-NH2 was found to be the most potent inactivator with a second order rate constant of 840±90 M-1s-1. Fragmentation of the complexes by using cyanogen bromide and trypsin followed by liquid chromatog./ESI-MS confirmed the identity of the adduct and allowed inhibitor mass differences of as little as 6 Da to be distinguished in a single experiment This approach allows the rapid screening and identification of preferred covalent inhibitors or intermediates from combinatorial libraries without deconvolution or resynthesis and should be applicable to irreversible inhibitors of virtually any enzyme that uses a covalent catalysis mechanism.

REFERENCE COUNT: 25 THERE ARE 25 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

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YOU HAVE REQUESTED DATA FROM 7 ANSWERS - CONTINUE? Y/(N):y

L30 ANSWER 14 OF 20 BIOSIS COPYRIGHT 2004 BIOLOGICAL ABSTRACTS INC. on STN
ACCESSION NUMBER: 2004:44315 BIOSIS
DOCUMENT NUMBER: PREV200400045266
TITLE: Single-chain recombinant complexes of **hepatitis**

**C** virus NS3 **protease** and NS4A cofactor peptide.
AUTHOR(S): **Malcolm, Bruce A.** [Inventor, Reprint Author]; Taremi, S. Shane [Inventor]; Weber, Patricia C. [Inventor]; Yao, Nanhua [Inventor]
CORPORATE SOURCE: Upper Montclair, NJ, USA
ASSIGNEE: Schering Corporation
PATENT INFORMATION: US 6653127 November 25, 2003
SOURCE: Official Gazette of the United States Patent and Trademark Office Patents, (Nov 25 2003) Vol. 1276, No. 4. http://www.uspto.gov/web/menu/patdata.html. e-file. ISSN: 0098-1133 (ISSN print).
DOCUMENT TYPE: Patent
LANGUAGE: English
ENTRY DATE: Entered STN: 14 Jan 2004
Last Updated on STN: 14 Jan 2004
AB Covalent HCV NS4A-NS3 complexes comprising the central hydrophobic domain of native HCV NS4A peptide, a linker, and the HCV NS3 serine **protease** domain, wherein the hydrophobic domain of native HCV NS4A peptide is tethered by the linker to the amino terminus of the HCV NS3 **protease** domain.

L30 ANSWER 15 OF 20 BIOSIS COPYRIGHT 2004 BIOLOGICAL ABSTRACTS INC. on STN
ACCESSION NUMBER: 2003:98332 BIOSIS
DOCUMENT NUMBER: PREV200300098332
TITLE: Quantitative estimation of viral fitness using PyrosequencingTM.
AUTHOR(S): Lahser, Frederick C.; Wright-Minogue, Jacquelyn; Skelton, Angela; **Malcolm, Bruce A.** [Reprint Author]
CORPORATE SOURCE: Department of Antiviral Therapy, Schering-Plough Research Institute, Kenilworth, NJ, 07033, USA bruce.malcolm@spcorp.com
SOURCE: BioTechniques, (January 2003) Vol. 34, No. 1, pp. 26-28. print. ISSN: 0736-6205 (ISSN print).
DOCUMENT TYPE: Article
LANGUAGE: English
ENTRY DATE: Entered STN: 12 Feb 2003
Last Updated on STN: 12 Feb 2003

L30 ANSWER 16 OF 20 BIOSIS COPYRIGHT 2004 BIOLOGICAL ABSTRACTS INC. on STN
ACCESSION NUMBER: 2001:439366 BIOSIS
DOCUMENT NUMBER: PREV200100439366
TITLE: Single-chain recombinant complexes of **hepatitis C** virus NS3 **protease** and NS4A cofactor peptide.
AUTHOR(S): **Malcolm, Bruce A.** [Inventor]; Taremi, S. Shane [Inventor, Reprint author]; Weber, Patricia C. [Inventor]; Yao, Nanhua [Inventor]
CORPORATE SOURCE: Upper Montclair, NJ, USA
ASSIGNEE: Schering Corporation
PATENT INFORMATION: US 6211338 April 03, 2001
SOURCE: Official Gazette of the United States Patent and Trademark Office Patents, (Apr. 3, 2001) Vol. 1245, No. 1. e-file. CODEN: OGUPE7. ISSN: 0098-1133.
DOCUMENT TYPE: Patent
LANGUAGE: English
ENTRY DATE: Entered STN: 19 Sep 2001
Last Updated on STN: 22 Feb 2002
AB Covalent HCV NS4A-NS3 complexes comprising the central hydrophobic domain

of native HCV NS4A peptide, a linker, and the HCV NS3 serine **protease** domain, wherein the hydrophobic domain of native HCV NS4A peptide is tethered by the linker to the amino terminus of the HCV NS3 **protease** domain.

L30 ANSWER 17 OF 20 BIOSIS COPYRIGHT 2004 BIOLOGICAL ABSTRACTS INC. on STN
ACCESSION NUMBER: 2001:186506 BIOSIS
DOCUMENT NUMBER: PREV200100186506
TITLE: Effect of naturally occurring active site mutations on **hepatitis C** virus NS3 **protease** specificity.
AUTHOR(S): Beyer, Brian M.; Zhang, Rumin; Hong, Zhi; Madison, Vincent; **Malcolm, Bruce A.** [Reprint author]
CORPORATE SOURCE: Schering-Plough Research Institute, 2015 Galloping Hill Road, Kenilworth, NJ, 07033, USA
bruce.malcolm@spcorp.com
SOURCE: Proteins, (May 1, 2001) Vol. 43, No. 2, pp. 82-88. print.
CODEN: PSFGEY. ISSN: 0887-3585.
DOCUMENT TYPE: Article
LANGUAGE: English
ENTRY DATE: Entered STN: 20 Apr 2001
Last Updated on STN: 18 Feb 2002

AB A comparison of the DNA sequences from all available genotypes of HCV indicate that the active site residues of the NS3 **protease** are strictly conserved with the exception of positions 123 and 168, which border the S4 subsite. In genotype 3, the canonic arginine and aspartic acid have been replaced with threonine and glutamine, respectively. To determine if these differences contribute to an altered specificity, we characterized single-chain NS3 **proteases** from strains 1a, 1b, and 3a with peptide substrates and product inhibitors on the basis of the natural cleavage junction sequences, in addition to polyprotein substrates derived from the 1a strain. No statistically significant differences in specificity were observed. To demonstrate that the active sites were actually different, we generated and evaluated peptide substrates with unnatural extended side-chains. These studies confirmed that there are measurable differences between the NS3 **proteases** of genotypes 1 and 3. Specifically, a 5-fold difference in Ki was observed between the **proteases** from genotypes 1 and 3 when a D-Glu occupied P5, and a 30-fold difference was seen when this position contained a D-homoglutamate. The contribution of residues 123 and 168 toward the altered specificity was then evaluated individually by site-directed mutagenesis. These mutants showed that potency differences within this series could be attributed to the residue that occupied position 123 of the **protease.** Modeling these unnatural substrate/mutant **protease** interactions, on the basis of cocrystal structures of enzyme-substrate complexes, provides a structural basis for these observations.

L30 ANSWER 18 OF 20 BIOSIS COPYRIGHT 2004 BIOLOGICAL ABSTRACTS INC. on STN
ACCESSION NUMBER: 1999:294327 BIOSIS
DOCUMENT NUMBER: PREV199900294327
TITLE: A novel recombinant single-chain **hepatitis C** virus NS3-NS4A protein with improved helicase activity.
AUTHOR(S): Howe, Anita Y. M. [Reprint author]; Chase, Robert; Taremi, S. Shane; Risano, Christine; Beyer, Brian; **Malcolm, Bruce**; Lau, Johnson Y. N.
CORPORATE SOURCE: Schering-Plough Research Institute, K-15-4-E4945, 2015 Galloping Hill Road, Kenilworth, NJ, 07033, USA
SOURCE: Protein Science, (June, 1999) Vol. 8, No. 6, pp. 1332-1341.

print.
ISSN: 0961-8368.
DOCUMENT TYPE: Article
LANGUAGE: English
ENTRY DATE: Entered STN: 5 Aug 1999
Last Updated on STN: 5 Aug 1999

AB **Hepatitis C** virus (HCV) nonstructural protein 3 (NS3) has been shown to possess **protease** and helicase activities and has also been demonstrated to spontaneously associate with nonstructural protein NS4A (NS4A) to form a stable complex. Previous attempts to produce the NS3/NS4A complex in recombinant baculovirus resulted in a protein complex that aggregated and precipitated in the absence of nonionic detergent and high salt. A single-chain form of the NS3/NS4A complex (His-NS4A21-32-GSGS-NS33-631) was constructed in which the NS4A core peptide is fused to the N-terminus of the NS3 **protease** domain as previously described (Taremi et al., 1998). This protein contains a histidine tagged NS4A peptide (a.a. 21-32) fused to the full-length NS3 (a.a. 3-631) through a flexible tetra amino acid linker. The recombinant protein was expressed to high levels in Escherichia coli, purified to homogeneity, and examined for NTPase, nucleic acid unwinding, and proteolytic activities. The single-chain recombinant NS3-NS4A protein possesses physiological properties equivalent to those of the NS3/NS4A complex except that this novel construct is stable, soluble and sixfold to sevenfold more active in unwinding duplex RNA. Comparison of the helicase activity of the single-chain recombinant NS3-NS4A with that of the full-length NS3 (without NS4A) and that of the helicase domain alone suggested that the presence of the **protease** domain and at least the NS4A core peptide are required for optimal unwinding activity.

L30 ANSWER 19 OF 20 BIOSIS COPYRIGHT 2004 BIOLOGICAL ABSTRACTS INC. on STN
ACCESSION NUMBER: 1999:299494 BIOSIS
DOCUMENT NUMBER: PREV199900299494
TITLE: A continuous spectrophotometric assay for the **hepatitis C** virus serine **protease**
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AUTHOR(S): Zhang, Rumin; Beyer, Brian M.; Durkin, James; Ingram, Richard; **Njoroge, F. George**; Windsor, William T.; **Malcolm, Bruce A.** [Reprint author]
CORPORATE SOURCE: Schering-Plough Research Institute, 2015 Galloping Hill Rd., Kenilworth, NJ, 07033, USA
SOURCE: Analytical Biochemistry, (June 1, 1999) Vol. 270, No. 2, pp. 268-275. print.
CODEN: ANBCA2. ISSN: 0003-2697.
DOCUMENT TYPE: Article
LANGUAGE: English
ENTRY DATE: Entered STN: 12 Aug 1999
Last Updated on STN: 12 Aug 1999

AB The **hepatitis C** virus (HCV) encodes a chymotrypsin-like serine **protease** responsible for the processing of HCV nonstructural proteins and which is a promising target for antiviral intervention. Its relatively low catalytic efficiency has made standard approaches to continuous assay development only modestly successful. In this report, four continuous spectrophotometric substrates suitable for both high-throughput screening and detailed kinetic analysis are described. One of these substrates, Ac-DTEDVVP(Nva)-O-4-phenylazophenyl ester, is hydrolyzed by HCV **protease** with a second-order rate constant (kcat/Km) of 80,000 +- 10,000 M-1 s-1. Together with its negligible rate of nonenzymatic hydrolysis under assay conditions (0.01 h-1), analysis of as little as 2 nM **protease** can be completed in under 10 min.

L30 ANSWER 20 OF 20 BIOSIS COPYRIGHT 2004 BIOLOGICAL ABSTRACTS INC. on STN
ACCESSION NUMBER: 1998:494577 BIOSIS
DOCUMENT NUMBER: PREV199800494577
TITLE: Construction, expression, and characterization of novel fully activated recombinant single-chain **hepatitis C** virus **protease.**
AUTHOR(S): Taremi, S. Shane; Beyer, Brian; Maher, Maureen; Yao, Nanhua; Prosise, Winifred; Weber, Patricia C.; **Malcolm, Bruce A.** [Reprint author]
CORPORATE SOURCE: Schering-Plough Res. Inst., 2015 Galloping Hill Rd., Kenilworth, NJ 07033, USA
SOURCE: Protein Science, (Oct., 1998) Vol. 7, No. 10, pp. 2143-2149. print.
ISSN: 0961-8368.
DOCUMENT TYPE: Article
LANGUAGE: English
ENTRY DATE: Entered STN: 18 Nov 1998
Last Updated on STN: 18 Nov 1998

AB Efficient proteolytic processing of essential junctions of the **hepatitis C** virus (HCV) polyprotein requires a heterodimeric complex of the NS3 bifunctional **protease**/helicase and the NS4A accessory protein. A single-chain recombinant form of the **protease** has been constructed in which NS4A residues 21-32 (GSVVIVGRIILS) were fused in frame to the amino terminus of the NS3 **protease** domain (residues 3-181) through a tetrapeptide linker. The single-chain recombinant **protease** has been overexpressed as a soluble protein in E. coli and purified to homogeneity by a combination of metal chelate and size-exclusion chromatography. The single-chain recombinant **protease** domain shows full proteolytic activity cleaving the NS5A-5B synthetic peptide substrate, DTEDVVCCSMSYTWTGK with a Km and kcat of 20.0 +- 2.0 muM and 9.6 +- 2.0 min -1, respectively; parameters identical to those of the authentic NS31-631 /NS4A1-54 protein complex generated in eukaryotic cells.

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